Novel insights into heart failure with preserved ejection fraction

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PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Wednesday 13 January 2016 at 14.30 hours

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INTRODUCTION AND OVERVIEW

INTRODUCTION AND OVERVIEW*

Heart failure with preserved ejection fraction (HFpEF) currently represents one of the greatest unmet needs in Cardiology. Barely 25 years ago, we did not believe that heart failure could exist in the presence of an apparently normal ejection fraction. We now know that HFpEF not only exists and can be diagnosed, but that it currently constitutes half the heart failure population in many parts of the world and will become the predominant type of heart failure in future. Furthermore, it is a highly morbid and deadly disease. Most significantly, our attempts to extrapolate proven therapies in heart failure with reduced ejection fraction (HFrEF) to this population have uniformly failed to improve outcomes in HFpEF, and in fact, this is a syndrome for which we still do not have any effective therapy.

The controversies surrounding HFpEF is reflected in the transition of nomenclature used to refer to it, from diastolic heart failure to heart failure with normal systolic function, heart failure with normal ejection fraction, and now heart failure with preserved EF.(1) This evolution also reflects our increasing understanding of this important syndrome.

Understanding HFPEF: An evolution of nomenclature

Perhaps the purest description of this syndrome was the first by Topol et al in 1985,(2) where the term "***hypertensive hypertrophic cardiomyopathy of the elderly***" was used to describe 21 elderly, predominantly female hypertensive patients with HF symptoms, left ventricular (LV) hypertrophy, high EF, and diastolic dysfunction. Robust epidemiologic evidence has confirmed that this is a condition predominantly affecting elderly hypertensive women.

The term "***diastolic HF***" was coined to underscore the hallmark of LV diastolic dysfunction seen in most, if not all, patients. The diastolic/systolic HF distinction became popular as it was easy to use, neatly divided the HF world into two halves, and reflected the leading pathophysiologic factor believed to cause each syndrome. However, population-based studies showed that LV diastolic dysfunction was present in a large proportion of adults without HF, and that patients

with “systolic HF” were even more likely to have diastolic dysfunction compared to patients with so-called “diastolic HF”.

Thus entered the term “***HF with normal systolic function (HFNSF)***” – a term that did not make assumptions regarding underlying disease mechanisms and could therefore accommodate emerging evidence of pathophysiologic processes extending beyond diastolic dysfunction to vascular, atrial, pulmonary, right-sided and non-cardiovascular organ (eg renal) dysfunction. However, HFNSF was deemed suboptimal when it became apparent that systolic function was not necessarily normal in these patients, and that myocardial contractile dysfunction existed despite normal overall chamber pump function.

The term “***HF with normal EF (HFNEF)***” was then embraced and adopted in guidelines. However, EF is a continuous variable with a normal distribution within the population, and the threshold value to define “normal” versus “reduced” EF is arbitrary. Indeed, Framingham Heart Study participants with EF 40-50% were at greater risk of HF and death compared to those with EF>50%,(3) and distinct physiologic differences were described among Chinese with HF and EF>55% versus EF 40%-55%.(4)

Furthermore, the “normal” distribution shifts in the very population most affected by this syndrome: data from MESA(5) has shown that EF “normally” rises with age and is higher in women than men in the general population. The key issue is that EF is a fraction, which will increase as the heart remodels and the LV end-diastolic volume (denominator) shrinks out of proportion to the stroke volume (numerator). This begs the question, what is the normal EF in an elderly female patient who has HF? If “normal” is a higher EF in these patients, then by using an age- and sex- neutral cutoff of 50% to define HFNEF, we are effectively selecting for elderly women who actually have “relatively abnormal” EF for their age and sex. By extrapolation, this concept may apply to all individuals with smaller heart sizes (smaller LV end-diastolic volumes) – not just women (versus men) or those with concentrically remodeled ventricles (elderly, hypertensives), but also individuals of smaller body size in general.

One may stop here and argue that we should not be looking

at EF in the first place.(1) However the most significant counter-argument to this is that clinical trials using EF to stratify HF have revealed two phenotypes that respond differently to the same therapy: renin-angiotensin-aldosterone system blockade improves survival in HFrEF but not in HFNEF. Any classification that can guide treatment would be useful in clinical practice; a well-accepted example being the classification of myocardial infarction into ST-elevation versus non-ST-elevation myocardial infarction, as opposed to the outdated terminology Q-wave versus non-Q-wave myocardial infarction. Although we still have a long way to go before we understand the pathophysiologic differences between HFrEF and HFNEF as deeply as we do for ST-elevation versus non-ST-elevation myocardial infarction, recent studies have been revealing and continue to demonstrate differences at the cardiac chamber and ultra-structural levels, as well as the hemodynamic response to therapeutic interventions. Until we can effectively tease apart pathophysiologic subtypes in HF using a different classification system of proven utility for clinical management and targeted therapy, we are left with our current system of using EF. Hence the case for the term "***HF with preserved EF (HFpEF)***", which makes no assumptions regarding what a normal EF is, and is now used in current international guidelines. The papers that follow in this thesis adopts the prevailing paradigm at the time of writing, with the most recent papers using the term "HFpEF".

Overview of thesis

This thesis is structured in 4 parts: it starts with describing the epidemiology of HEpEF; progresses to an exploration of the potential pathophysiological mechanisms underlying HFpEF, and in-depth examination of why elderly hypertensive women are particularly at risk of HFpEF; and ends with a discussion of the clinical implications of current findings and important areas for future research.

Following this introduction, chapter 2 describes the epidemiology of HFpEF, including both known and unknown elements of the prevalence, incidence, risk factors, clinical presentation, clinical course and prognosis of the syndrome. This chapter importantly forms the basis of understanding the patient population and identifying the gaps

in knowledge that need to be addressed in more in-depth mechanistic studies.

In chapter 3, a unique approach is adopted in which epidemiologic data are used to interrogate mechanistic pathways underlying HFpEF. Here, population-based data from echocardiography and circulating biomarkers are used to characterize the cardiac structural changes, hemodynamic disturbances, and even systemic processes that contribute to HFpEF, by comparing HFpEF patients with age-, sex- and comorbidity- matched controls without heart failure.

Chapter 4 combines the key observations of chapter 2 (striking female predisposition to HFpEF) and chapter 3 (role of ventricular-vascular stiffening in HFpEF). By studying sex differences in HFpEF, further insights are provided into the central mechanisms that cause a predominant HFpEF phenotype in predisposed individuals, in contrast to a predominant HFrEF phenotype in other individuals (e.g. men with macrovascular coronary artery disease).

Finally in chapter 5, the findings of chapters 2, 3 and 4 are brought to the patient's bedside in a comprehensive discussion on the clinical implications for patient management, as well as identification of the key unanswered questions and remaining controversies that need to be addressed in future research.

REFERENCES

*Adapted from From: **Lam CS**, Pieske B. Heart Fail Clin. 2014 Jul;10(3):xv and **Lam CS**. JACC Heart Fail. 2014 Oct;2(5):541-3

1. Sanderson JE. HFNEF, HFpEF, HF-PEF, or DHF: What Is in an Acronym? JACC Heart Fail. 2014 Feb;2(1):93-4.
2. Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. N Engl J Med. 1985 Jan 31;312(5):277-83.
3. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation. 2003 Aug 26;108(8):977-82.
4. He KL, Burkhoff D, Leng WX, Liang ZR, Fan L, Wang J, et al. Comparison of ventricular structure and function in Chinese patients with heart failure and ejection fractions >55% versus 40% to 55% versus <40%. Am J Cardiol. 2009 Mar 15;103(6):845-51.
5. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2009 May;2(3):191-8.

Chapter 2

Epidemiology of heart failure with preserved ejection fraction

2.1. Epidemiology and clinical course of heart failure with preserved ejection fraction.

Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Eur J Heart Fail. 2011 Jan;13(1):18-28

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ABSTRACT

Heart Failure with Preserved Ejection Fraction (HFPEF) is increasingly recognized as a major public health problem worldwide. Significant advances have been made in our understanding of the epidemiology of HFPEF over the last two decades, with the publication of numerous population-based epidemiologic studies, large heart failure registries and randomized clinical trials. These recent studies have provided detailed characterization of larger numbers of patients with HFPEF than ever before. This review summarizes the state of current knowledge with regards to the disease burden, patient characteristics, clinical course and outcomes of HFPEF. Despite the wealth of available data, substantive gaps in knowledge were identified. These gaps represent opportunities for further research in HFPEF, a syndrome that is clearly a rising societal burden and that is associated with substantial morbidity and mortality.

INTRODUCTION

Heart failure (HF) affects about 2% of the western population, with the prevalence increasing sharply from 1% in 40-year-old individuals to 10% above the age of 75 years. It is the most common cause of hospitalization in patients over 65 years of age.(1-3) HF is defined as a syndrome characterized by an impaired ability of the heart to fill with and/or to eject blood commensurate with the metabolic needs of the body, resulting in a classical constellation of signs or symptoms of pulmonary and systemic venous congestion.(1)

While traditionally associated with the concept of “pump failure” or reduced left ventricular (LV) ejection fraction, it has become widely recognized that HF can occur even when ejection fraction is preserved, constituting the syndrome of HF with preserved ejection fraction (HFPEF). Several criteria have been proposed to define the syndrome of HFPEF,(2, 4, 5) the most comprehensive of which are the guidelines by the Echocardiography and Heart Failure Associations of the European Society of Cardiology.(2) In general these diagnostic criteria share three features in common: 1. Clinical signs or symptoms of HF; 2. Evidence of normal LV systolic function; and 3. Evidence of abnormal LV diastolic dysfunction.

Prevalence

The reported prevalence of preserved LVEF among patients with HF varied widely from 13% to 74% in early studies,(6) depending partly on sample inclusion criteria (including the choice of a 'normal' EF cut-point) and clinical settings. These selection biases were addressed in recent population-based echocardiographic investigations performed in large community-based samples in the United States (Olmsted County Study,(7) Cardiovascular Health Study,(8) Strong Heart Study,(9)), Portugal (EPICA Study(10)), the Netherlands (Rotterdam Study,(11) United Kingdom,(12) Sweden (Vasteras Study,(13) Finland (the Helsinki Aging Study),(14)) and Spain (Asturias Study(15)). Together, these recent studies provided a more refined estimate of the prevalence of HFPEF among patients with HF, which averaged 54%, with a range from 40% to 71%.(16) Inherent difficulties in making an accurate diagnosis of HFPEF, the lack of standardization of diagnostic criteria and the potential for misdiagnosis in these often elderly, overweight or deconditioned patients limit the precision of these estimates.(17) Nonetheless, the "true" overall prevalence of HFPEF in the community has been estimated at 1.1% to 5.5% of the general population.(16)

Of note, the prevalence of HFPEF in the community increased with advancing age, and was higher in women; the reported age- and sex- specific prevalence rose from 0 (men) -1% (women) in the age group 25-49 years to about 4-6% in men and 8-10% in women for individuals eighty years and older.(10) Further, the relative prevalence of HFPEF among all HF patients increased over time in a large hospital-based study in Olmsted County, Minnesota, rising from 38% to 54% (of all HF cases) between 1987 and 2001.(18) This temporal trend for increasing HFPEF occurred in association with increases in the prevalence of hypertension, diabetes and atrial fibrillation, but without a corresponding increase in the relative prevalence of HF with reduced ejection fraction (HFREF). In the same time frame, survival was noted to improve in patients with HFREF, but not in those with HFPEF. These secular trends underscore the importance of HFPEF as a major and growing public health problem.

Incidence

Few population-based studies have examined the temporal trends in the incidence of all HF in the community, regardless of ejection fraction, etiology or clinical setting. In the Framingham Heart Study,(19) the incidence of HF remained unchanged in men but declined in women between 1950 and 1999. In Olmsted County, MN,(20) the incidence of HF did not change between 1979 and 2000 among either men or women. In both samples, the survival after onset of HF improved over time in both men and women. With the aging of the population and improved survival after HF onset, we can expect a dramatic increase in cases of HF (prevalence) in spite of the stable incidence rates (Figure 1). In fact, recent statistical data from the American Heart Association(21) indicate that the annual actual caseload of HF may have exceeded this projected "epidemic". To date, no study has looked specifically at trends in incidence of HFPEF in the community. However, extrapolating from the observations in all HF patients, and assuming that half the caseload of HF consists of HFPEF, one can project an equal, if not greater, increase in HFPEF burden in the future.

Demographic features and risk factors

Recent large epidemiologic studies characterizing more than 57,000 HF patients have helped to confirm observations from previous smaller studies of selected patients(6), and more clearly define the demographic features of patients with HFPEF (Table 1). In general, these patients are older women with a history of hypertension. The prevalence of other cardiovascular risk factors varies depending on the study setting and the diagnostic criteria for the condition. Although not uniformly reported, cardiovascular risk factors are highly prevalent in HFPEF in population-based studies and registries, and include obesity in 41-46%, coronary artery disease in 20-76%, diabetes mellitus in 13-70%, atrial fibrillation (AF) in 15-41% and hyperlipidemia in 16-77%. In studies that included both HFPEF and HFREF,(18, 22-27) patients with HFPEF were consistently found to be older, more often female, more predominantly hypertensive and have a higher prevalence of atrial fibrillation but a lower prevalence of coronary artery disease compared to those with HFREF. Notably, non-cardiovascular co-

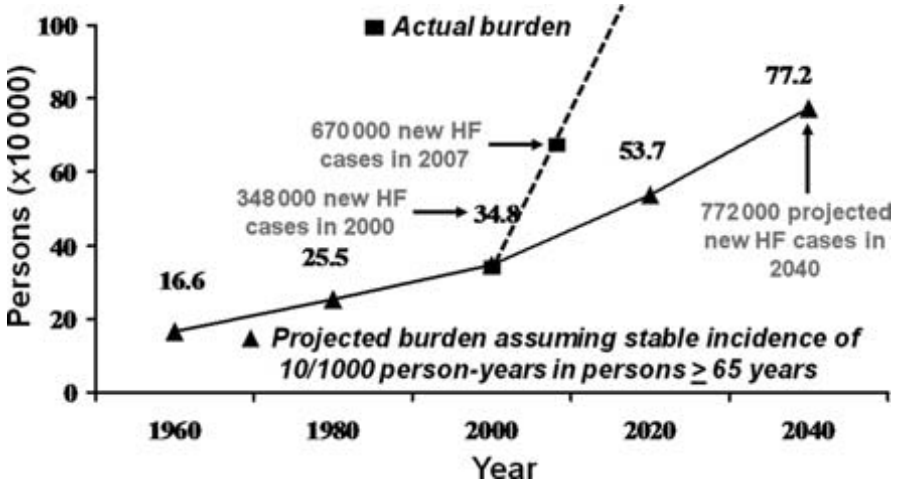

Figure 1. Burden of heart failure The actual annual incidence of heart failure reported in the United States (squares and dotted line) exceeded the projected annual incidence (triangles and solid line) calculated based on a stable incidence of 10 per 1000 person-years in persons aged ≥65 years.(21) Reproduced with permission from Reference 21.

morbidities also appear to be highly prevalent in HFPEF, consistent with an elderly population, and include renal impairment, chronic lung diseases, anemia, cancer, liver disease, peptic ulcer disease and hypothyroidism. The Charlson index,(28) a weighted prognostic score of co-morbidity , was reported in 2 studies indicating high co-existing disease burden (mean score=2.8(29) and score ≥3 in 70% of HFPEF patients(23)). Controlled clinical trials have, to date, included more than 10,000 HFPEF patients; the demographic characteristics and risk factor profiles of these individuals more closely resemble that of population-based studies in the more recently completed trials (I-PRESERVE, SENIORS, HK DHF, PEP-CHF) (Table 1).

Echocardiographic and hemodynamic features

In the most recent set of diagnostic criteria proposed by the European Society of Cardiology,(2) echocardiographic and hemodynamic features are key components for the diagnosis of HFPEF. After first establishing the presence of signs or symptoms of HF, the presence of an EF >50% and a LV end-diastolic volume index <97 mL/m² is the second essential criterion for the diagnosis.(2) The third criterion is the presence of LV diastolic dysfunction, which can be demonstrated by Doppler

Table 1: Demographic characteristics and risk factors in patients with HFPEF from recent studies

Study (Ref)	Setting	N with HF-PEF	Age	%Women	%Obesity (or mean BMI/ weight)	%Hypertension	%Coronary artery disease	%Diabetes mellitus	%Atrial fibrillation	%Renal impairment* (or mean creatinine)	%Hyperlipidemia* (or mean cholesterol)	Non-cardiovascular comorbidity
POPULATION-BASED STUDIES												
Lee DS, et al.(22)	Framingham Heart Study, Framingham MA, United States	220	80	65	(BMI=27 kg/m^2)	59	37	22	29	-	(TC=218 mg/dl)	
Bursi F, et al.(23)	Rochester Epidemiology Project, Olmsted County MN, United States	308	77	57	(BMI=29.6 kg/m^2)	86	36	36	31	11% with severe renal dysfunction (Creatinine clearance=54.2 ml/min)	77	38% COPD; 53% anemia; 70% Charlson index≥3
Owan TE, et al.(18)	Olmsted County MN, United States	2167	74	56	41 (BMI=29.7 kg/m^2)	63	53	33	41	(Creatinine=1.6 mg/dl)	-	Mean Hb=11.8 g/dl
Bhatia RS, et al.(24)	EFFECT Study, Ontario, Canada	880	75	66	-	55	36	32	32	22% with Creatinine>150 mmol/l; 1% on dialysis	16	12% cancer; 18% COPD; 8% peptic ulcer disease; 2% hepatitis/ cirrhosis; 21% anemia; 24% hyponatremia
Gottdiener JS, et al.(55)	Cardiovascular Health Study, Multicenter, United States	170	75	56	-	59	58	27	15	(Creatinine=1.2 mg/dl)	(TC=197 mg/dl)	FEV1=1.75 l/min
Devereux RB et al.(9)	Strong Heart Study, American Indian reservations, United States	50	64	84	(BMI=33.1 kg/m^2)	76	20	70	-	(Creatinine=2.3 mg/dl)	(LDL=103 mg/dl)	-
Yip GW, et al.(73)	Hong Kong, SAR, China	132	73 (including non-HFPEF)	55	-	57	39	35	-	9% end-stage renal failure	-	-
HF REGISTRIES												
OPTIMIZE-HF Fonarow GC et al.(25)	Acute HF from 259 hospitals across the United States	21149	75	62	(Weight=78.9 kg)	76	38	38	33	(Creatinine=1.3 mg/dl)	32	-
ADHERE Yancy CW, et al.(26)	Acute HF from >274 hospitals across the United States	26322	74	62	-	77	50	45	21	26	-	31% COPD or asthma
EuroHeart Failure Survey Lenzen MJ, et al.(27)	Acute HF from 115 hospitals in 24 European countries	3148	71	55	-	59	59	26	25	5	-	-
New York HF Registry Klapholz M, et al.(41)	HF hospitalizations from 17 centres in metropolitan New York, United States	619	72	73	46 (BMI=30.6 kg/ m^2)	78	43	46	23	4.5% dialysis (GFR=50.8 ml/min)		25% COPD or asthma; 10% hypothyroidism; mean Hb=11.8 mg/dl
UK-HEART MacCarthy PA, et al.(74)	Chronic HF from 4 centres in the United Kingdom	163	63	28	-	6	76	-	-	-	-	-
DIAMOND-CHF Gustafsson F, et al.(75)	Hospital-based multicentre trial screening registry, Denmark	2218	73	49	(BMI=26.4 kg/m^2)	25	49	13	26	2%, 24%, and 34% with creatinine clearance<20, 21-40 and 41-60 ml/min respectively	-	26% COPD
MISCHF Philbin EF, et al.(29)	Acute HF from 10 community hospitals in upstate New York, United States	312	75	70	(Weight=77 kg)	49	23	33	29	(Creatinine=1.5 mg/dl; creatinine clearance=57 ml/min)	-	Charlson Index=2.8
CONTROLLED CLINICAL TRIALS												
SENIORS van Veldhuisen DJ, et al.(76)	11 countries in Europe	752	76	50		78	77	24	36	Excluded significant renal dysfunction	47	-

I-PRESERVE	25 countries in Europe, America,	4128	72	60	41	88	25	27	29	30% with GFR<60 ml/ min/1.73 m²	-	12% anemia
Massie BM, et al.(50)	South Africa, Australia	150	74	62	(BMI~27 kg/m²)	82	15	20	16	-	9	-
HK DHF	Hong Kong SAR, China											
Yip GW, et al.(77)												
PEP-CHF	53 centres in Bulgaria, Czech	850	76	55	(BMI~27.5 kg/m²)	79	27	21	20	Creatinine=97 umol/l	-	-
Cleland JG, et al.(49)	Republic, Hungary, Ireland, Poland, Russia, Slovakia, United Kingdom											
Ancillary DIG	302 centres in the United States	988	67	41	(BMI=29 kg/m²)	62	50	27	Excluded	48% with GFR<60 ml/ min/1.73 m²		-
Ahmed A, et al.(56)	and Canada											
SWEDIC	12 hospitals in Sweden	113	67	43	(Weight=58-125 kg)	66	11	14	-	-	-	-
Bergstrom A, et al.(78)												
CHARM-Preserved	618 centres in 26 countries	3023	67	40	-	64	44	28	29	Excluded creatinine≥3 mg/dl (265 mmol/l)	-	7% cancer
Yusuf S, et al.(51)												

*variously defined as detailed below
BMI, body mass index; TC, total cholesterol; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; GFR, glomerular filtration rate; LDL, low density lipoprotein

echocardiography, cardiac catheterization or blood natriuretic peptide measurements. Using Doppler echocardiography, a ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity (E/e') exceeding 15 provides evidence for raised LV filling pressures. If the E/e' ratio is ≤ 8, then LV filling pressures are probably 'normal'. If the E/e' ratio is intermediate (>8-<15), it may be necessary to consider a multi-parametric approach using "second line" indices: the left atrial volume (> 40 ml/m²), LV mass index (>122 g/m2 in women and >149 g/m2 in men), mitral inflow Doppler (ratio of early to late mitral inflow velocity <0.5 and deceleration time >280 ms), pulmonary venous flow velocity patterns (duration of pulmonary venous A-wave reversal >30 ms longer than duration of mitral A-wave), or the presence of AF.

The utility of these "second line" indices was evaluated in a retrospective study of patients referred to a tertiary echocardiography laboratory,(30) where left atrial enlargement was shown to distinguish patients with E/e'>15 from those with E/e'<8 with better diagnostic accuracy than LV mass index or Doppler measurements. However, prospective evaluation is still needed in patients with confirmed clinical HF and E/e' in the intermediate range of 8-15.(31) Recognizing that advanced age and hypertension may be associated with changes in echocardiographic diastolic indices even in the absence of HF,

patients with HFPEF (HF by Framingham criteria and EF>50%) were compared to elderly hypertensive and healthy controls without HF from the general community in Olmsted County, MN.(32) While the extent of LV hypertrophy was similar in HFPEF and hypertensive controls, there was greater left atrial enlargement and higher estimated LV filling pressures (based on E/e' ratio) in HFPEF compared to both control groups, adjusting for age and sex. The E/e' ratio distinguished HFPEF from hypertensive controls without HF with better accuracy than left atrial volume index,(33) but the best diagnostic utility was observed with Doppler-estimated pulmonary artery systolic pressure in the Olmsted County cohort. Further, increasing pulmonary artery systolic pressure was associated with increasing mortality in HFPEF.(33) Similarly recognizing that age, sex, co-morbidities and LV structural remodeling can all affect circulating natriuretic peptide levels, plasma B-type natriuretic peptide (BNP) concentrations were compared between HFPEF and controls without HF in the former Olmsted County population-based study, adjusting for these covariates.(32) Plasma BNP concentrations were found to be elevated in HFPEF, consistent with findings in the large patient sample of the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial, in which plasma N-terminal(NT)-proBNP levels were also found to be raised in HFPEF.(34) The analysis from I-PRESERVE further showed that the elevation of circulating NT-proBNP was related to severity of symptoms/ functional status as well as to the baseline characteristics indicative of poorer outcomes in HFPEF.(34)

Invasive measurements of LV filling pressures remain the gold standard for diagnosis of HFPEF and should be considered in cases of diagnostic uncertainty. Cardiac catheterization is also useful for the assessment of pulmonary hypertension, which is common in HFPEF patients and may be related to both post-capillary pulmonary venous hypertension(35, 36) as well as a reactive pre-capillary component of pulmonary arterial hypertension.(33) An emerging area of interest is a reduction in the longitudinal component of LV systolic function (relatively easy to measure by echocardiography, Figure 2)(37) The reduction in longitudinal component of LV systolic function is compensated by a preserved/robust radial, circumferential and twist components that

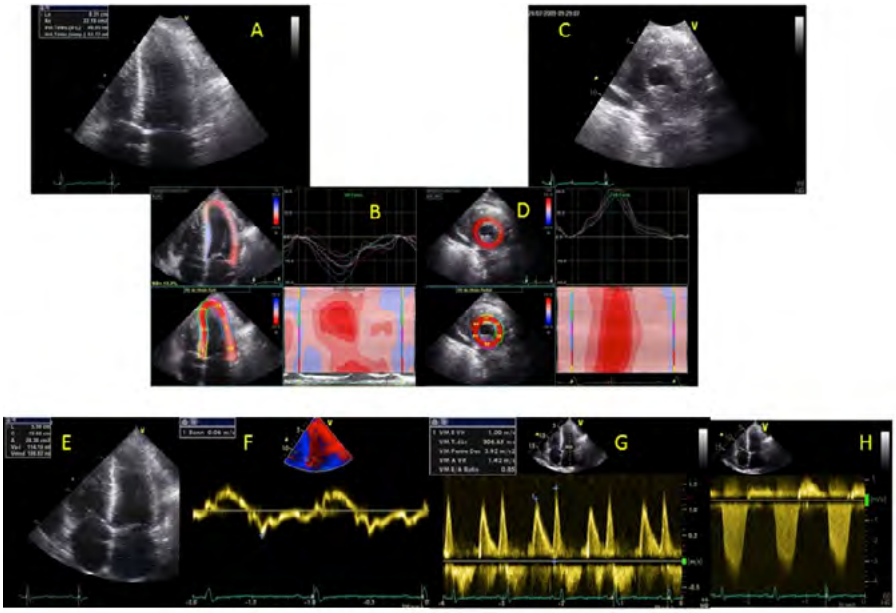

Figure 2. A patient diagnosed for a heart failure with preserved ejection fraction
A : apical 4-chamber view: left ventricular concentric hypertrophy with a small end-systolic volume. B: deformation imaging performed from this apical view to assess the longitudinal systolic function: the global longitudinal strain is depressed (-12.3%; normal -20%) despite the fact that the left ventricular ejection fraction is 55±5%. C: parasternal short axis view. D: radial strain assessment from this parasternal view: the radial strain is increased (60%, normal value 40%) to compensate for the decrease of the longitudinal one.. E: apical 4 chamber view: the left atrium is enlarged with a left atrial value greater than 38ml/M². F: pulse tissue Doppler demonstrating the e' is blunted (6cm/s) as s' is (other demonstration of the decrease in the left ventricular longitudinal function).G: mitral inflow: delayed relaxation pattern with E/e'> 13. H: tricuspid regurgitation with an estimated systolic pulmonary arterial pressure of ~ 55mmHg

are necessary to maintain a normal LVEF.(38, 39) Whether this can aid the diagnosis of HFPEF warrants validation in larger prospective studies of patients with suspected HFPEF. The potential contribution of mechanical asynchrony to the pathophysiology of HFPEF is also currently being evaluated.(40)

In summary, noninvasive hemodynamic assessment by comprehensive echocardiographic evaluation is recommended in patients with suspected HFPEF. Plasma biomarker measurement (natriuretic peptides) may aid the diagnosis but in equivocal cases, invasive assessment should be considered.

Clinical course

Large prospective national registries have consistently demonstrated that 46-51% of hospitalized acute heart failure patients have a preserved LV ejection fraction.(25-27) These patients are also just as likely to be re-admitted following discharge as patients with HFREF, with a re-hospitalization rate of 29% within 60-90 days,(25) and a median time to re-hospitalization of 29 days.(27)

The clinical factors precipitating acute decompensation versus the chronic syndrome of HFPEF have been systematically examined in a few studies.(22, 41-43) Of the clinical risk factors highly prevalent in HFPEF (discussed under “Demographic features and risk factors” above), a few have been consistently identified in these studies to be associated with episodes of acute decompensation: Uncontrolled hypertension is a frequent presenting feature of acute HFPEF. The role of hypertension is underscored by recent large registries of acutely decompensated HFPEF showing raised admission blood pressure (mean systolic blood pressure 149 mmHg(25) and 153 mmHg(26)) and high proportions of patients with uncontrolled systolic hypertension at presentation (12% with uncontrolled hypertension,(25) 61% with systolic blood pressure >140 mmHg(26)). Interestingly, whereas systolic blood pressures were higher, mean diastolic blood pressures in both registries were lower in patients with acute HFPEF compared to patients with HFREF, suggesting the presence of widened pulse pressures and possible arterial stiffening in these patients. Another important potentially reversible precipitating factor for HFPEF is AF. This arrhythmia was found on the initial presenting ECG in 21% of acutely decompensated HFPEF patients in the ADHERE registry.(26) Indeed, these findings lend support to treatment guidelines advocating judicious blood pressure and rhythm control in HFPEF. Further, the potential contribution of non-cardiovascular factors (such as lung disease, renal impairment or sepsis(41, 42)) to acute HFPEF decompensation deserves mention, an observation consistent with the high prevalence of co-morbid conditions in these elderly patients (Table 1).

Overall mortality rates in HFPEF

Several studies have evaluated the short- and long-term mortality of HFPEF, compared these mortality patterns with that of HFREF, and assessed the prognostic factors that determine mortality risk in patients with HFPEF. In general, mortality rates have varied substantially across studies of HFPEF in part because of the heterogeneity in the diagnosis of the condition(44) (variability in EF cut points used, the requirement for demonstrating presence of diastolic dysfunction or meeting recent criteria for HFPEF advocated by the European Society of Cardiology(2)), differing sampling strategies and study designs (observational cohort versus clinical trial versus hospital-based registries), biases introduced by exclusion of HF patients with missing EF,(45) and possible temporal trends in mortality patterns.(46) Nonetheless, most studies have consistently demonstrated higher mortality rates in HFPEF patients compared to age- and sex-matched controls without HF in the community.

HFPEF is associated with high in-hospital, short-term and long-term mortality rates. In studies that have evaluated mortality during the peri-hospitalization period, the in-hospital mortality rates have ranged from 3-6.5% during the index hospitalization.(25, 47, 48) Short-term (30-90-day) mortality also is high, ranging typically between 5-9.5%.(24, 25) The long-term mortality rates seem more variable in the reported literature. Thus, annualized mortality rates ranged from about 3.5%-6% in 3 of the large randomized clinical trials(49-51) to about 15% in the observational community-based Framingham Study.(22) The lower mortality of HPEF patients in clinical trials likely reflects a selection bias favoring relatively younger, more compliant individuals with a lesser co-morbidity burden. A recent meta-analysis(45) of 7688 patients with HFPEF followed for about 4 years noted an overall mortality of 32% mortality, averaging to about an 8% annual mortality rate. The longer-term (5-year) mortality rates across observational studies and registries evaluating prevalence cohorts of HFPEF are consistently high, although absolute rates have varied considerably from about 55%(46, 52) to 74%.(22)

Comparison of mortality rates with HFREF

Numerous investigations have compared long-term mortality rates in patients with HFPEF and HFREF. Several of the observational epidemiological cohort studies have consistently reported similar mortality rates in HFPEF and HFREF.(22, 46) On the other hand, clinical trials that included both kinds of HF patients have typically reported lower mortality in HFPEF compared to HFREF.(51, 53, 54) More recently, Somartane and colleagues(45) published the largest systematic meta-analytic comparison of death rates in the two kinds of HF; the investigators compared mortality in 7688 HFPEF patients with 16,831 HFREF patients from 17 studies, and noted a 50% lower hazard for mortality in HFPEF compared to HFREF.(45) The strengths of this meta-analysis was that it included only studies where all HF patients had an EF measured; as noted above, missing EF is an important source of bias when one compares mortality rates in HFPEF versus HFREF.(45) It is worth noting that notwithstanding the reported higher mortality of HFREF, given the aging of the population and the preponderance of HFPEF in the elderly, the overall absolute number of deaths in the community attributable to HFPEF is likely higher than the number of deaths attributable to HFREF.(55)

Table 2. Proportions of deaths due to cardiovascular versus non-cardiovascular mortality in HFPEF patients according to study design.

Study (Ref)	Design	% Non-cardiovascular deaths	% Cardiovascular deaths
Henkel DM, et al.(46)	Community-based cohort	49	51
Tribouilloy C, et al.(52)	Population based, hospitalized patients	41	59
Grigorian-Shamagian L, et al.(57)	single tertiary care hospital	20	80
Yusuf S, et al.(51)	Clinical trial	28	72
Ahmed A, et al.(56)	Clinical trial	30	70
Massie BM, et al.(50)	Clinical trial	30	70
Zile MR, et al. (58)	Clinical trial	30	60*

*Cardiovascular deaths including 26% sudden death, 14% heart failure, 5% myocardial infarction, and 9% stroke; unknown mode of death in 10% in this trial

Patterns of mortality in HFPEF: cardiovascular versus non-cardiovascular mortality

As noted above, there is a general consensus that patients with HFPEF have high co-morbidity burden due to their elderly nature. The proportion of deaths attributed to cardiovascular versus non-cardiovascular causes in HFPEF varies with study design, mode of death ascertainment, and time period of the studies (Table 2).(46, 50-52, 56, 57) Thus, a recent report from the Mayo Clinic(46) (that was community-based, and in which the cause of death was adjudicated by a coroner) underscored that nearly half of HFPEF patients succumbed to non-cardiovascular diseases, and there has been a temporal trend for higher non-cardiovascular mortality in HFPEF in the most recent decade (late 1990s-early 2000). Overall, community-based studies(46, 52, 57) demonstrate a higher proportion of non-cardiovascular deaths, and clinical trials(50, 51, 56, 58) report a higher % of cardiovascular deaths (Table 2). This pattern may reflect the enrollment of healthier patients with fewer co-morbidities in controlled clinical trials. Cardiovascular causes of death in HFPEF patients include sudden death, refractory HF (pump failure), myocardial infarction and other cardiovascular disease (stroke or coronary disease).(46, 50-52, 56-58) When cause-specific mortality patterns are compared between HFPEF and HFREF, the latter has a higher burden of cardiovascular-related death compared to the former.(46)

HFPEF prognostic factors for mortality risk

Several studies have examined the factors influencing mortality risk in HFPEF. Thus, in one of the larger series from Canada(24) that systematically investigated the impact of prognostic factors, the following factors increased mortality risk: older age, associated co-morbidities (presence of peripheral vascular disease, dementia or cancer each doubled mortality risk), worse clinical profile at presentation as reflected by anemia (Hb<10 g/dl), higher serum creatinine (>150 µmol/L), hyponatremia (<136 mmol/l), each of which increased mortality risk by 50%, and a lower systolic BP. Some other studies have emphasized a worse prognosis in men with HFPEF (compared to women),(59) those with diabetes,(60) chronic obstructive lung disease,(61) atrial

fibrillation,(62) a restrictive filling pattern.(63) The presence of diabetes increases the likelihood of cardiovascular-related death in HFPEF.(60)

Some recent investigations have evaluated if the paradigm of reverse epidemiology observed in HFREF is also evident in HFPEF. These studies have reported that lower BMI, lower SBP, and lower total cholesterol are all markers of increased mortality risk in HFPEF, thereby extending the reverse epidemiology concept beyond HFREF.(64, 65) The impact of etiology of HFPEF on mortality risk is less clear, with conflicting reports in the literature; a recent report noted similar mortality risk in HFPEF due to valve disease, hypertension or ischemic heart disease,(52) whereas another study(22) highlighted a worse prognosis in those with coronary disease as the basis of HFPEF.

In summary, HFEPF has a high mortality risk, on an average lower than HFREF, a higher likelihood of non-cardiovascular death, and a range of prognostic factors that are generally similar to those noted for HFREF.

Future Directions

As discussed above, several gaps exist in our knowledge of the epidemiology of HFPEF and represent potential areas for future study

Table 3. Unresolved issues in HFEPF epidemiology: Future directions for research

1. **Definition and diagnosis**
- Define optimal cut-point for normal left ventricular ejection fraction
Characterize epidemiology based on stricter adherence to diagnostic guidelines(2, 44)
Better characterize varying subsets of disease with different underlying pathophysiology
Better identify cut-points for natriuretic peptides to diagnose HF in patients with equivocal diagnostic criteria
Better define role of newer imaging metrics like long axis function, strain rate
Identify role of exercise testing in unmasking symptoms, signs and imaging features in patients with suspected HFPEF with equivocal rest studies
2. **Demographic and other clinical features/risk factors**
- Better data on incidence, prevalence, trends in the same, across regions and by ethnicity
- Clarify pathophysiologic basis for preponderance in women and elderly, including contributions of multiple non-cardiac organ systems dysfunction, family history, metabolic risk factors (including the metabolic syndrome)
- Delineate the role of risk factors such as atrial fibrillation, hypertensive crises in the natural progression of HFPEF
3. **Mortality patterns**
- Define mortality patterns in studies without selection bias and without missing echocardiograms on patients
- Delineate the contribution of cardiovascular versus non-cardiovascular deaths in patients with HFPEF

(Table 3). The diagnostic cut points that define a normal LVEF differ across the various studies of HFPEF, with ESC guidelines advocating a threshold of 50%.(2) However, this threshold remains arbitrary, and individuals with a LVEF in the range 50-54% may also potentially have systolic dysfunction.(66) Use of a higher cut-point for defining normal LVEF (55%) would lower the prevalence of HFPEF. Additional investigations describing the natural history of individuals with borderline LVEF (50-54%) may help to resolve this controversy. On a parallel note, the ESC guidelines advocate cut-points for circulating BNP and pro-BNP of 200 and 220 pg/ml respectively for substantiating a diagnosis of HF in patients with suspected HFPEF who have a normal LVEF but an equivocal E/e'.(2) However, given that women and elderly have higher BNP/proBNP levels, these cut-points likely have a greater negative than positive predictive value.(67) Further studies are warranted to identify optimal cut-points for natriuretic peptides to aid the diagnosis of HFPEF in equivocal cases.

Traditionally, HFPEF has been diagnosed based on a normal LVEF, but recent studies have noted the potential importance of abnormalities of the long axis LV function, LV strain and strain rate, torsion and asynchrony in addition to left atrial systolic and diastolic function.(38) Of note, measurement of global strain rate during the isovolumic relaxation period of the cardiac cycle has been advocated as a key diagnostic parameter in individuals with suspected HFPEF but non-diagnostic E/e' ratios.(38) Future prospective studies are needed to validate these newer measures against invasive gold standards and determine their impact on outcomes in HFPEF.(40, 68)

It is also noteworthy that well-compensated HFPEF patients may be asymptomatic at rest but may be prone to exercise-induced exacerbations of HF symptoms and elevations of LV filling pressures. The role of exercise testing for provocation of symptoms and /or diastolic (and systolic) dysfunction in suspected HFPEF patients needs to be better defined.(69) On a separate note, several investigators have questioned the need for demonstration of abnormal LV diastolic function itself for a diagnosis of HFPEF. Several non-diastolic mechanisms for HFPEF have been reviewed(70) and that include volume expansion, venoconstriction (altered venous capacitance), increased vascular

and ventricular stiffness indices, and chronotropic incompetence. This raises the notion that there are likely several distinct pathophysiological entities encompassed by the syndrome of HFPEF. Thus, describing the principal underlying substrates (diastolic dysfunction versus non-diastolic cardiac mechanisms; or systemic [non-cardiac] mechanisms; or combinatorial factors) may be an important component of the diagnostic strategy. Indeed, Paulus and van Ballegoji have recently opined that strict adherence to ESC diagnostic criteria for HFPEF may facilitate the characterization of specific homogeneous subgroups such as those with HF, concentric hypertrophy and arterial hypertension.(44)

Other gaps in knowledge pertain to the world-wide prevalence of HFPEF (beyond US and Europe) and variation in the burden of HFPEF according to ethnicity. Recent data indicate a potential greater burden of diastolic dysfunction in Africans of Caribbean descent,(71) highlighting the need for future studies of multi-ethnic samples. Given some suggestion of a rising incidence of HFPEF, longitudinal studies are needed to prospectively monitor incidence and prevalence of HFPEF, including assessment of temporal trends.

Several key clinical factors related to HFPEF merit further study. Thus, while a female preponderance for the condition is well known, additional investigations are necessary to identify factors that increase risk for HFPEF in women, including the relative contributions of their greater longevity, the lower burden of coronary disease, sex-related differences in LV remodeling in response to pressure-overload, hormonal factors, and sex-related differences in vascular function, venous capacitance, and susceptibility to volume overload. A family history of heart failure increases risk of the condition in offspring.(72) However, it is unclear if HFPEF aggregates within families, or if parental HFPEF elevates risk of the condition in the offspring, a premise that should be investigated further.(72) Given the high prevalence of obesity, dyslipidemia and diabetes mellitus in patients with HFPEF, investigations to elucidate the contribution of metabolic disturbances (including the metabolic syndrome) to the rising burden of HFPEF are warranted.

From a prevention perspective, further investigation of key precipitating factors for HFPEF in well-compensated individuals with

LV diastolic dysfunction is critical. For instance, the relations of AF and HF in HFPEF are likely complex; it is unclear in what proportion of individuals AF presages HFPEF, and vice versa. Likewise, given the frequent presence of elevated BP at presentation, studies to evaluate the contribution of exacerbations of pulsatile load on the heart to overt decompensation and to identify potential triggers for these BP escalations are warranted.

The sections above also have underscored the current challenges related to describing the mortality patterns in HFPEF. Additional studies without selection bias or missing LVEF data are necessary to fully characterize mortality patterns in HFPEF (overall rates and cardiovascular versus non-cardiovascular mortality), including comparisons with HFREF, and clarifying the impact of etiology of HFPEF on mortality risk. Well-designed studies are needed to ascertain the exact mode of death in these patients, and to better elucidate the contribution of the HF state itself to non-cardiovascular deaths in HFPEF patients. It is not clear if diastolic dysfunction or the HF state is a key contributor to likelihood of death due to non-cardiovascular causes.

In conclusion, major advances have been made in our understanding of the epidemiology of HFPEF over the last two decades, but substantive gaps still exist in our knowledge. These gaps present a window of opportunity for additional research delineating these less-studied aspects of HFPEF, a disorder characterized by substantial morbidity and mortality and a rising societal burden.

Acknowledgments.
This work was supported in part by National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. NO1-HC-25195).

REFERENCES

1. Jessup M, Brozena S. Heart failure. N Engl J Med 2003; 348(20):2007-2018.
2. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007; 28(20):2539-2550.
3. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26(11):1115-1140.
4. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000; 101(17):2118-2121.
5. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. Prog Cardiovasc Dis 2005; 47(5):314-319.
6. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995; 26(7):1565-1574.
7. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003; 289(2):194-202.
8. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001; 87(4):413-419.
9. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000; 86(10):1090-1096.
10. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, Oliveira A. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail 2002; 4(4):531-539.
11. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A,

Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. Eur Heart J 1999; 20(6):447-455.

12. Morgan S, Smith H, Simpson I, Liddiard GS, Raphael H, Pickering RM, Mant D. Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey. BMJ 1999; 318(7180):368-372.
13. Hedberg P, Lonnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I. Left ventricular systolic dysfunction in 75-year-old men and women; a population-based study. Eur Heart J 2001; 22(8):676-683.
14. Kupari M, Lindroos M, Iivanainen AM, Heikkila J, Tilvis R. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med 1997; 241(5):387-394.
15. Cortina A, Reguero J, Segovia E, Rodriguez Lambert JL, Cortina R, Arias JC, Vara J, Torre F. Prevalence of heart failure in Asturias (a region in the north of Spain). Am J Cardiol 2001; 87(12):1417-1419.
16. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis 2005; 47(5):320-332.
17. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from “diastolic heart failure” or from misdiagnosis? A prospective descriptive study. BMJ 2000; 321(7255):215-218.
18. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355(3):251-259.
19. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002; 347(18):1397-1402.
20. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. JAMA 2004; 292(3):344-350.
21. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association’s strategic Impact Goal through 2020 and beyond. Circulation; 121(4):586-613.
22. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation

2009; 119(24):3070-3077.

23. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. JAMA 2006; 296(18):2209-2216.
24. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006; 355(3):260-269.
25. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007; 50(8):768-777.
26. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006; 47(1):76-84.
27. Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J 2004; 25(14):1214-1220.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373-383.
29. Philbin EF, Rocco TA, Jr., Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. Am J Med 2000; 109(8):605-613.
30. Emery WT, Jadavji I, Choy JB, Lawrance RA. Investigating the European Society of Cardiology Diastology Guidelines in a practical scenario. Eur J Echocardiogr 2008; 9(5):685-691.
31. Handoko ML, Paulus WJ. Polishing the diastolic dysfunction measurement stick. Eur J Echocardiogr 2008; 9(5):575-577.
32. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007; 115(15):1982-1990.
33. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009; 53(13):1119-1126.
34. McKelvie RS, Komajda M, McMurray J, Zile M, Ptaszynska A, Donovan M, Carson P, Massie BM. Baseline plasma NT-proBNP and clinical

characteristics: results from the irbesartan in heart failure with preserved ejection fraction trial. J Card Fail; 16(2):128-134.

35. Hoeper MM, Barbera JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009; 54(1 Suppl):S85-96.
36. Puwanant S, Priester TC, Mookadam F, Bruce CJ, Redfield MM, Chandrasekaran K. Right ventricular function in patients with preserved and reduced ejection fraction heart failure. Eur J Echocardiogr 2009; 10(6):733-737.
37. Vinereanu D, Nicolaides E, Tweddel AC, Fraser AG. "Pure" diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. Eur J Heart Fail 2005; 7(5):820-828.
38. Wang J, Nagueh SF. Current perspectives on cardiac function in patients with diastolic heart failure. Circulation 2009; 119(8):1146-1157.
39. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008; 29(10):1283-1289.
40. Donal E, Lund LH, Linde C, Edner M, Lafitte S, Persson H, Bauer F, Ohrvik J, Ennezat PV, Hage C, Lofman I, Juilliere Y, Logeart D, Derumeaux G, Gueret P, Daubert JC. Rationale and design of the Karolinska-Rennes (KaRen) prospective study of dyssynchrony in heart failure with preserved ejection fraction. Eur J Heart Fail 2009; 11(2):198-204.
41. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, Kalman J, Phillips RA, Steingart R, Brown EJ, Jr., Berkowitz R, Moskowitz R, Soni A, Mancini D, Bijou R, Sehhat K, Varshneya N, Kukin M, Katz SD, Sleeper LA, Le Jemtel TH. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 2004; 43(8):1432-1438.
42. Chen HH, Lainchbury JG, Senni M, Bailey KR, Redfield MM. Diastolic heart failure in the community: clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. J Card Fail 2002; 8(5):279-287.
43. Kramer K, Kirkman P, Kitzman D, Little WC. Flash pulmonary edema: association with hypertension and reoccurrence despite coronary revascularization. Am Heart J 2000; 140(3):451-455.
44. Paulus WJ, van Ballegoij JJ. Treatment of Heart Failure With Normal Ejection Fraction An Inconvenient Truth! J Am Coll Cardiol 2010; 55(6):526-537.
45. Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley

GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. Eur J Heart Fail 2009; 11(9):855-862.

46. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail 2008; 1(2):91-97.
47. Perez de Isla L, Zamorano J, Hernandez N, Contreras L, Rodrigo JL, Almeria C, Aubele AL, Mataix L, Macaya C. Prognostic factors and predictors of in-hospital mortality of patients with heart failure with preserved left ventricular ejection fraction. J Cardiovasc Med (Hagerstown) 2008; 9(10):1011-1015.
48. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, Kato N, Takeshita A, Tsutsui H. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009; 73(10):1893-1900.
49. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006; 27(19):2338-2345.
50. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008; 359(23):2456-2467.
51. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362(9386):777-781.
52. Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy F, Peltier M, Slama M, Massy Z. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008; 29(3):339-347.
53. Davis BR, Kostis JB, Simpson LM, Black HR, Cushman WC, Einhorn PT, Farber MA, Ford CE, Levy D, Massie BM, Nawaz S. Heart failure with preserved and reduced left ventricular ejection fraction in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Circulation 2008; 118(22):2259-2267.
54. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003; 362(9386):759-766.
55. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons:

influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002; 137(8):631-639.

56. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Jr., Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006; 114(5):397-403.
57. Grigorian-Shamagian L, Otero Ravina F, Abu Assi E, Vidal Perez R, Teijeira-Fernandez E, Varela Roman A, Moreira Sayagues L, Gonzalez-Juanatey JR. Why and when do patients with heart failure and normal left ventricular ejection fraction die? Analysis of >600 deaths in a community long-term study. Am Heart J 2008; 156(6):1184-1190.
58. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation; 121(12):1393-1405.
59. Alla F, Al-Hindi AY, Lee CR, Schwartz TA, Patterson JH, Adams KF, Jr. Relation of sex to morbidity and mortality in patients with heart failure and reduced or preserved left ventricular ejection fraction. Am Heart J 2007; 153(6):1074-1080.
60. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J 2008; 29(11):1377-1385.
61. Rusinaru D, Saaidi I, Godard S, Mahjoub H, Battle C, Tribouilloy C. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. Am J Cardiol 2008; 101(3):353-358.
62. Fung JW, Sanderson JE, Yip GW, Zhang Q, Yu CM. Impact of atrial fibrillation in heart failure with normal ejection fraction: a clinical and echocardiographic study. J Card Fail 2007; 13(8):649-655.
63. Independence of restrictive filling pattern and LV ejection fraction with mortality in heart failure: an individual patient meta-analysis. Eur J Heart Fail 2008; 10(8):786-792.
64. Guder G, Frantz S, Bauersachs J, Allolio B, Wanner C, Koller MT, Ertl G, Angermann CE, Stork S. Reverse epidemiology in systolic and nonsystolic heart failure: cumulative prognostic benefit of classical cardiovascular risk factors. Circ Heart Fail 2009; 2(6):563-571.
65. Kapoor JR, Heidenreich PA. Obesity and survival in patients with heart failure and preserved systolic function: a U-shaped relationship. Am Heart

J; 159(1):75-80.

66. Mahadevan G, Davis RC, Frenneaux MP, Hobbs FD, Lip GY, Sanderson JE, Davies MK. Left ventricular ejection fraction: are the revised cut-off points for defining systolic dysfunction sufficiently evidence based? Heart 2008; 94(4):426-428.
67. Maeder MT, Kaye DM. Heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 2009; 53(11):905-918.
68. Donal E, Lund LH, Oger E, Edner M, Persson H. What are the true prognostic differences between heart failure with preserved and reduced ejeciton fraction? Eur J Heart Fail 2010.
69. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009; 54(1):36-46.
70. Bench T, Burkhoff D, O'Connell JB, Costanzo MR, Abraham WT, St John Sutton M, Maurer MS. Heart failure with normal ejection fraction: consideration of mechanisms other than diastolic dysfunction. Curr Heart Fail Rep 2009; 6(1):57-64.
71. Sharp A, Tapp R, Francis DP, Mc GTSA, Hughes AD, Stanton AV, Zambanini A, Chaturvedi N, Byrd S, Poulter NR, Sever PS, Mayet J. Ethnicity and left ventricular diastolic function in hypertension an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy. J Am Coll Cardiol 2008; 52(12):1015-1021.
72. Lee DS, Pencina MJ, Benjamin EJ, Wang TJ, Levy D, O'Donnell CJ, Nam BH, Larson MG, D'Agostino RB, Vasan RS. Association of parental heart failure with risk of heart failure in offspring. N Engl J Med 2006; 355(2):138-147.
73. Yip GW, Ho PP, Woo KS, Sanderson JE. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. Am J Cardiol 1999; 84(5):563-567.
74. MacCarthy PA, Kearney MT, Nolan J, Lee AJ, Prescott RJ, Shah AM, Brooksby WP, Fox KA. Prognosis in heart failure with preserved left ventricular systolic function: prospective cohort study. BMJ 2003; 327(7406):78-79.
75. Gustafsson F, Torp-Pedersen C, Brendorp B, Seibaek M, Burchardt H, Kober L. Long-term survival in patients hospitalized with congestive heart failure: relation to preserved and reduced left ventricular systolic function. Eur Heart J 2003; 24(9):863-870.
76. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left

ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol 2009; 53(23):2150-2158.

77. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, Yip T, Lau ST, Lau CP, Tang MO, Yu CM, Sanderson JE. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart 2008; 94(5):573-580.
78. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail 2004; 6(4):453-461.

Chapter 2

Epidemiology of heart failure with preserved ejection fraction

2.2. How do patients with heart failure with preserved ejection fraction die?

Chan MM, Lam CS. Eur J Heart Fail. 2013 Jun;15(6):604-13

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ABSTRACT

Understanding how patients with heart failure with preserved ejection fraction (HFPEF) die provides insight into the natural history and pathophysiology of this complex syndrome, thereby allowing better prediction of response to therapy in designing clinical trials. This review summarizes the current state of knowledge surrounding mortality rates, modes of death and prognostic factors in HFPEF. Despite lack of uniform reporting, the following conclusions may be drawn from prior studies: The mortality burden of HFPEF is substantial, ranging from 10-30% annually, and higher in epidemiologic studies than clinical trials. Mortality rates compared to heart failure with reduced ejection fraction (HFREF) appear strongly influenced by the type of study, but are clearly elevated compared to age- and comorbidity-matched controls without heart failure. The majority of deaths in HFPEF are cardiovascular deaths, comprising 51-60% of deaths in epidemiologic studies, and ~70% in clinical trials. Among cardiovascular deaths, sudden death and heart failure death are the leading cardiac modes of death in HFPEF clinical trials. Compared to HFREF, the proportions of cardiovascular deaths, sudden death and heart failure deaths are lower in HFPEF. Conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFPEF than HFREF, particularly in epidemiologic studies, where this difference may be related to fewer coronary heart deaths in HFPEF. Key mortality risk factors, including age, gender, body mass index, burden of comorbidities and coronary artery disease, offer some explanation for the differences in mortality rates observed across studies.

INTRODUCTION

The importance of understanding how patients with heart failure with preserved ejection fraction (HFPEF) die goes far beyond morbid fascination. Epidemiologic trends show that the prevalence of HFPEF relative to heart failure with reduced ejection fraction (HFREF) is increasing over time; yet at the same time survival in HFPEF has remained dismal whereas prognosis has improved in HFREF.1, 2In fact, all outcome trials in HFPEF to date have failed to demonstrate survival benefit, despite robust evidence of prognostic benefit using the same

agents in HFREF. The continued absence of guideline-recommended proven therapies for HFPEF may directly impact outcomes in patients with HFPEF,3 but also importantly points to large gaps in knowledge of therapeutic targets and raises the issue of whether we are measuring the right outcomes in HFPEF trials. Do we really understand how patients with HFPEF die? What is their risk of death in absolute terms, as well as relative to age- and comorbidity-matched adults or patients with HFREF? Do these elderly patients die of the disease itself (i.e. heart failure), related cardiovascular causes (e.g. myocardial infarction) or age-associated non-cardiovascular causes (e.g. cancer)? In other words, do they die with or of HFPEF (analogous to the case with prostate cancer in elderly men, who often die with, but not of, prostate cancer)? What are the factors that contribute to death in HFPEF? Can we expect targeted therapies to influence all-cause mortality, and if not, what cause-specific outcomes are most appropriately studied? We aim to explore these issues in this review, using available data to date.

WHAT IS THE RISK OF DEATH IN HFPEF?

Several studies have examined mortality in HFPEF, usually in comparison with HFREF (Table 1).

Effect of type of study

Depending on the study design (randomized controlled trials [RCT] versus population-based studies) and selection criteria (left ventricular ejection fraction [LVEF] criteria, hospitalized versus outpatients, number of comorbidities), different HFPEF populations have been sampled, potentially explaining some of the discrepancies amongst reported outcomes.4-6In epidemiologic community-based studies, the 1-year mortality rate of HFPEF was almost 30%.2 In RCTs, mortality rates 2-3 times lower have been reported (1-year mortality ~10%),7-10 a difference that may be partially attributed to selection bias (younger population, better compliance to therapy and lower burden of comorbidities in RCTs). In terms of absolute mortality rates, a recent meta-analysis of 31 studies (both observational studies and RCTs) showed that the pooled death rate in HFPEF was 121 (95% confidence interval [CI]: 117, 126) deaths per 1000 patient-years in all the studies;

Table 1. Characteristics and mortality rates of recent studies reporting outcomes in HFPEF. Dx - diagnosis; ECHO - echocardiography; HF Hosp - heart failure hospitalization; LVEF - left ventricular ejection fraction; NT-proBNP - N-terminal pro B-type natriuretic peptide; NYHA -

Study (Study period)	Setting	HFPEF No.	LVEF criteria	Inclusion Criteria	Key Exclusion Criteria	Follow-up duration (years)	Ave. Annual Mortality Rate (%)
Population-based Studies							
Adabag *et al.*[29] (1995-2000)	22 hospitals. USA.	787	≥ 45%	Index HF hosp.		5	10
Owan *et al.*[2] (1987-2001)	Mayo Clinic Hospital USA.	2167	≥ 50%	Index HF hosp. + ECHO in ≤30 days		10	13
Bhatia *et al.*[15] (1999-2001)	103 hospitals. Canada.	880	> 50%	Index HF hosp.		1	22.2
Perez de Isla *et al.*[53] (2002-2003)	Single centered hospital. Spain.	679	≥ 50%	≥ 70 years Index HF hosp. Clinical & radiographic dx of HF		1.5	25.4
Randomized Clinical Trials							
I-PRESERVE[9] (2002-2005)	25 Countries. Europe, USA, South Africa & Australia	4128	≥ 45%	≥ 60 yrs NYHA ≥ II HF hosp. ≤6 mths	SBP <100 or >160mmHg. DBP >95mmHg. Hb<11g/dL.	4	5.20
DIG-PEF[8] (1991-1993)	USA (186 centers) Canada (116 centers)	988	> 45%	LVEF >45% Sinus Rhythm at baseline	Cor pulmonale	3	7.6
CHARM-Preserved[10] (1999-2000)	618 centers in 26 countries.	3022	> 40%	≥18 years NYHA II–IV ≥4wks Previous hosp for cardiac reason	Persistent systolic or diastolic hypertension	3	5.00
PEP-CHF[7] (2000-2003)	53 centers in 8 countries.	846	> 40%	≥70 yrs 3 of 9 clinical symptoms + 2 of 4 ECHO parameters	Significant valve disease Stroke history.	2.2	5.90
TIME-CHF[19] (2004)	15 hospitals. Switzerland & Germany.	123	> 45%	≥ 60 yrs NYHA ≥II Hx HF hosp. ≤1 yr NT-proBNP level 2xUL of norm.		1.5	14
National Heart Failure Registries							
Heart Failure Survey in Israel (HFSIS).[16] (2003)	25 hospitals. Israel.	1364	≥ 40%	Clinical dx of HF Confirmed by ECHO & radiography.		1	22
Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD).[14] (2009)	164 hospitals. Japan.	429	≥ 50%	HF as primary cause of hosp.		2.4	11.60

New York Heart Association Classification; UL – upper limit.

146 (95% CI: 138, 154) deaths per 1000 patient-years in non-RCTs alone; and 101 (95% CI: 96, 107) deaths per 1000 patient-years in the RCTs alone.11 In aggregate, it is clear that the mortality burden of HFPEF is substantial regardless of setting, but has been reported to be higher in 'real world' compared to clinical trial settings.

Effect of hospitalization

Studies have also examined short- and long-term mortality rates following hospitalization for HFPEF. In-hospital mortality rates have ranged from 2.5-6.5% with similar or lower risks compared to HFREF.12-14Short-term mortality ranged from 30-day rates of 5.3%,1560- to 90-day rates of 9.5%12and 6-month rates of 14.2-16%.16, 17Published long-term 5-year mortality rates varied from 22-65%.2, 18

The over-riding message from these studies is that the mortality rate in hospitalized HFPEF is high. There appears to be similar mortality rates between HFPEF versus HFREF up to 6 months following hospitalization, after which HFPEF patients may display a better survival probability.

Comparison to HFREF

Reported mortality rates in comparison with HFREF are strongly influenced by the type of study from which mortality data are derived. Epidemiologic community-based studies demonstrated similar prognosis between both patient groups,2, 15whereas a meta-analysis inclusive of RCTs showed ~32% higher survival in HFPEF than HFREF (pooled hazards ratio 0.68; 95% CI: 0.64, 0.71).11Of note, there was a highly significant interaction between type of HF (HFPEF versus HFREF) and the type of study (RCT versus non-RCT) on risk of death, where survival was ~39% higher in HFPEF than HFREF in the RCTs, but only ~24% higher in HFPEF than HFREF in the non-RCTs. Interestingly, the mortality gap between HFPEF and HFREF appeared to be diminished among the very elderly.19

Comparison to age- and comorbidity- matched patients

The lower mortality of HFPEF compared to "conventional" heart failure (i.e. HFREF) in controlled trials, presence of multiple age-

related comorbidities, and non-specificity of symptoms of HFPEF, have given rise to two controversies: Firstly, do patients enrolled in HFPEF trials truly have the syndrome of HFPEF, or are they misdiagnosed cases (of, for example, lung disease, obesity or myocardial ischemia)?20Secondly, is HFPEF a distinct disease entity, or does it merely represent a collection of comorbidities in an elderly breathless patient?21The potential for misdiagnosis of HFPEF is clinically relevant and an important consideration particularly in earlier trials such as CHARM-Preserved, where patients were enrolled solely on the basis of symptoms and signs of HF (and normal EF), with or without a history of recent HF hospitalization, and in the absence of additional echocardiographic or biomarker criteria.10 In fact, Caruana et al.20showed that alternative non-HF diagnoses were available that could explain patients' symptoms and signs in the majority of cases in their cohort of suspected HFPEF from general practice.

A misdiagnosis of HFPEF would be expected to contribute to a lower proportion of cardiovascular deaths.22However, when Campbell et al.23compared mortality in patients from RCTs of HFPEF (including CHARM-Preserved, DIG-PEF and I-PRESERVE) to patients with similar age, gender and comorbidity distribution in other cardiovascular trials of hypertension (ALLHAT, LIFE, ANBP-2, VALUE and HYVET), coronary heart disease (ACTION) and diabetes mellitus (ACCORD), patients with HFPEF were found to have a significantly higher proportion of cardiovascular deaths compared to non-HFPEF patients. Furthermore, overall mortality rates were found to be strikingly higher in HFPEF trial patients (53-76 per 1000 patient-years) compared to non-HFPEF trial patients (11-47 per 1000 patient-years), despite a lower comorbidity burden in HFPEF than non-HFPEF trial patients. Thus, even acknowledging the potential for misdiagnosis, the substantially worse prognosis of patients with HFPEF compared to patients with hypertension and other cardiovascular risk factors but without HF, suggests that HFPEF is not merely about old age and comorbidities; instead, HFPEF is an entity in itself that identifies patients at an elevated risk of death.

In the community-based setting, Mohammed et al.24compared survival, as well as cardiovascular parameters adjusted for comorbidities

and scaled for body size and age, in patients with HFPEF, age-/gender-matched healthy controls and hypertensive controls without heart failure. While each comorbidity was associated with a unique ventricular-vascular profile and impacted survival in HFPEF, the presence of HFPEF itself was associated with further cardiovascular changes that could not be accounted for by comorbidities alone. These findings thus supported the conclusion that HFPEF was a distinct disease rather than an amalgamation of comorbidities, and provided a basis to understand the worse survival in patients with HFPEF compared to age- and comorbidity-matched patients without heart failure.

HOW DO PATIENTS WITH HFPEF DIE?

Importance of defining how patients with HFPEF die

Although several studies have examined outcomes in HFPEF, few have reported specific causes or modes of death. Why is it important to drill down to specifics? As discussed above, multiple age-related comorbidities may co-exist in patients with HFPEF, and each comorbidity may impart a mortality risk. Knowledge of all-cause mortality alone will not allow discernment of risk related to the comorbidity versus risk associated with HFPEF itself. Knowledge of cause-specific mortality, on the other hand, will aid our understanding of the pathophysiology and natural history of HFPEF as a distinct syndrome, and allow better discernment of risk that may be prevented or treated, versus that which cannot. This knowledge then forms the basis for planning and predicting the impact of interventional strategies. Take for instance a patient with HFPEF who suffers an acute myocardial infarction (cause of death [COD]) leading to sudden death (mode of death [MOD]), versus one with severe infective exacerbation of concomitant chronic lung disease (COD) leading to respiratory collapse (MOD). An intervention such as an implantable cardiac defibrillator would be expected to prevent death in the former, but not the latter, and knowledge of the relative proportions of deaths from each cause/mode in HFPEF would guide decisions on whether defibrillators should be considered or tested as a therapeutic strategy in this patient population.

Challenges in the classification of death in HFPEF

Comprehensive clinical data are needed for the accurate classification of death in HFPEF. A previously published ACME system for death in heart failure is a useful guideline for the extent of information required to draw meaningful inferences:25A for activity and place of death (outpatient or in-hospital), C for COD (e.g. myocardial infarction, ventricular dysfunction or pneumonia), M for MOD (e.g. sudden death or circulatory failure) and E for events associated with death (e.g. recent hospitalizations or de-compensations). Without a priori planning, such detailed information is rarely available to allow accurate classification of death.

CODs are more commonly reported in epidemiologic studies, where data are extracted from death certificates, medical records and autopsy findings. Reliability of the data is increased when death ascertainment is carried out by autopsy findings or a chief medical examiner; however this is available on a large scale in only few communities.26MODs are more readily available in RCTs, where there is regular surveillance and formal adjudication of deaths by appointed outcome review committees using pre-specified criteria.

There is a lack of uniformity in definitions used to classify deaths in HFPEF in previous publications. To illustrate, mortal events have been grouped under subheadings of sudden death (MOD) and acute myocardial infarction (COD) within the same table, without distinguishing MOD versus COD.9, 27Some other studies have also reported events according to the underlying versus immediate causes of death, rather than COD and MOD.28

Cardiovascular versus non-cardiovascular deaths in HFPEF

Notwithstanding the variability of definitions used in different studies, the following conclusions can be derived from published outcomes studies in HFPEF (Figure 1): Firstly, the majority of deaths in HFPEF across all studies are cardiovascular deaths. Secondly, the proportion of cardiovascular deaths varies with the type of study, ranging from 51-60% in epidemiologic studies, to ~70% in RCTs. The only exception was the study by Adabag et al.29of HF hospitalizations in Minneapolis-St Paul, where 5-year post discharge mortality in HFPEF was classified

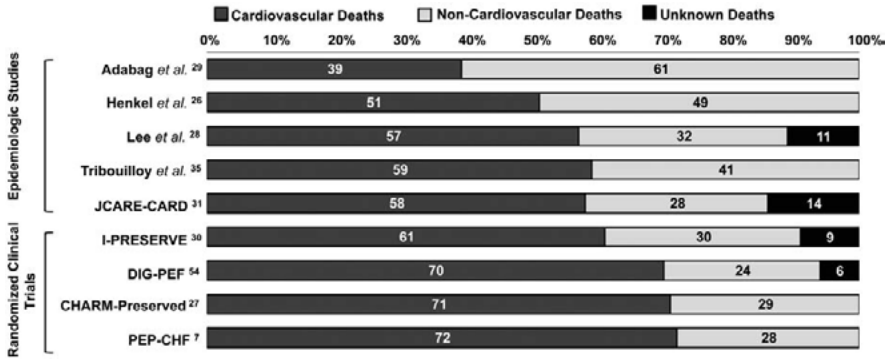

Figure 1. Distribution of mortal events in HFPEF studies. Bars and numbers indicate % of total deaths.Proportion of deaths attributed to cardiovascular, non-cardiovascular and unknown causes/modes from epidemiologic studies and randomized clinical trials.

based on death certificates as non-cardiovascular deaths in 61% of cases. Lack of autopsy data and selection bias due to large numbers of missing EF data, may have influenced these results. Nonetheless, the higher proportion of non-cardiovascular deaths in this observational study is consistent with the trend for more non-cardiovascular deaths in epidemiologic studies, compared to RCTs in HFPEF.

MOD in HFPEF

Specific MODs in HFPEF have been examined in the CHARM-Preserved and I-PRESERVE clinical trials (Figure 2).27, 30Despite some differences in the populations studied, remarkable consistency was observed in MODs reported: Among the ~70% majority of cardiovascular deaths, sudden death was the commonest cardiac MOD (26-28% of all deaths), followed by heart failure deaths (14-21% of all deaths).

COD in HFPEF

In epidemiologic studies, CODs are described, albeit inconsistently. Data from the large Olmsted County cohort, where COD was ascertained from death certificates, >75% of which were completed by coroner or Mayo staff, showed that the predominant single COD in this study was non-cardiovascular death. However, cardiovascular CODs as a group were more common than non-cardiovascular death, and the

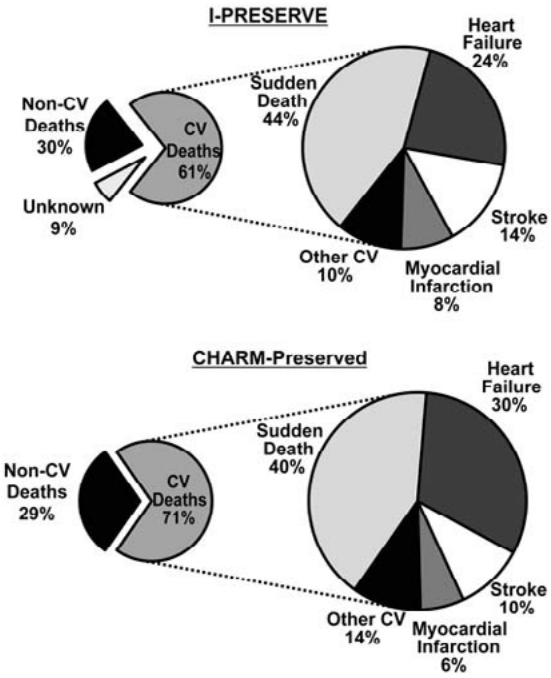

Figure 2. Distribution of modes of death in HFPEF clinical trials Numbers represent % of total deaths (left pie charts) and % of total cardiovascular deaths (right pie charts). The pie charts display the modes of death for patients from the I-PRESERVE trial30 (Top) and CHARM-Preserved trial27 (Bottom). Pie charts on the left display the proportion of cardiovascular (CV), non-cardiovascular (non-CV) and unknown deaths with respective % of total death. Further breakdown of cardiovascular deaths into sudden cardiac death, heart failure deaths, stroke, myocardial infarction and other cardiovascular deaths are shown in a separate pie chart on the right with respective % of cardiovascular death displayed.

most prominent cardiovascular COD was coronary heart disease (29% of all deaths).26

COD versus MOD in HFPEF

Both COD and MOD were specifically reported and directly compared in the recent TIME-CHF study, where outcomes were classified according to the ACME criteria after an 18-month follow-up.19Analysis of COD versus MOD in TIME-CHF showed differences in the proportions of cardiovascular-related events when classified by COD (~40%) versus MOD (~66%) (Figure 3). Careful inspection of the data revealed that this difference was primarily attributed to a larger proportion of “unknown” assignments for COD, with less “unknown” and more frequent

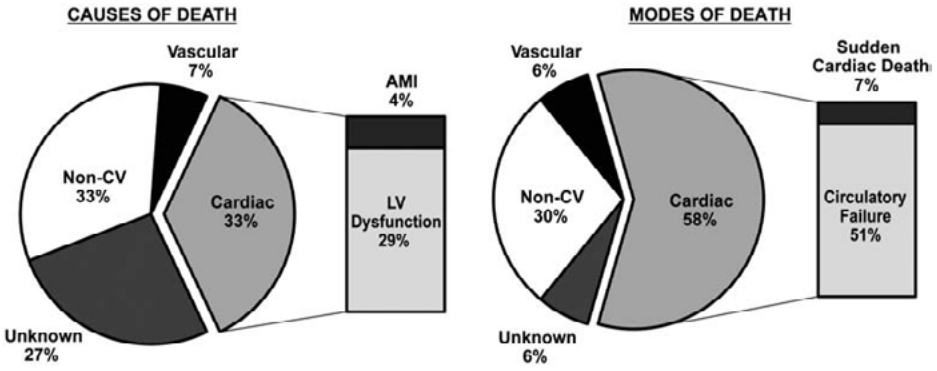

Figure 3. Effect of classification by causes versus modes of death in HFPEF (Adapted from TIME-CHF) All numbers represent approximate % of total deaths. Causes (left) and modes (right) of death reported in TIME-CHF.19 All deaths are separated into cardiac, vascular, non-cardiovascular (non-CV) and unknown deaths; Under causes of death, cardiac deaths are further separated into acute myocardial infarction (AMI) and left ventricular dysfunction (LV dysfunction). Under modes of death, cardiac deaths are further separated into sudden cardiac death or circulatory failure.

assignment of "cardiovascular" for MOD, and otherwise comparable classification of non-cardiovascular events by COD or MOD. These results highlight the challenges in classification of death, the limitations of comparisons across studies using different methods, and provide a possible source of discordance between observational studies (mainly reporting COD) and clinical outcome trials (mainly reporting MOD).

Classification of death in HFPEF versus HFREF

Cardiovascular deaths constitute the majority of deaths in both HFPEF and HFREF (Figure 4). However, the proportion of total deaths that are cardiovascular-related is higher in HFREF than HFPEF, whether considering data from RCTs (~80% versus ~70%),27,30 or community-based studies (~ 60% versus ~50%).26, 29, 31Conversely, non-cardiovascular deaths constitute a larger proportion of deaths in HFPEF than HFREF (~30% versus ~15% from RCTs; ~50% versus ~30% in community-based studies).

Specific MODs differ in their distribution between HFPEF and HFREF (Table 2). Sudden death and heart failure deaths constitute a larger proportion of deaths in HFREF compared to HFPEF. In fact, the leading single MOD in HFREF RCTs was sudden death (~42%),

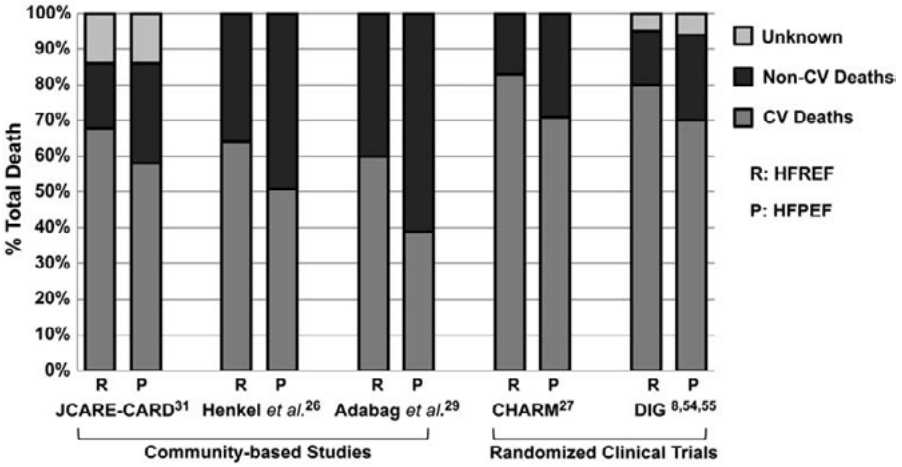

Figure 4. Distribution of deaths in HFPEF versus HFREF. Distribution of death into cardiovascular (CV), non-cardiovascular (non-CV) and unknown causes/modes from studies examining outcomes in HFPEF and HFREF.

whereas that in HFPEF was non-cardiovascular death (~30%) followed closely by sudden death (26-28%).30In epidemiologic studies from Olmsted County, the proportion of deaths attributed to coronary heart deaths was larger in HFREF (43%) than HFPEF (29%).26Of note, the lower proportion of coronary heart deaths in HFPEF appeared to account for the lower proportion of cardiovascular deaths, or the higher proportion of non-cardiovascular deaths, in HFPEF compared to HFREF. The Olmsted County study also showed that the proportion of cardiovascular deaths decreased from 69% in 1979–1984 to 40% in 1997–2002 (P=0.007) in HFPEF, in contrast to a modest trend in HFREF (77% to 64%, P=0.08). These observations raise the intriguing notion that HFPEF patients may be increasingly spared of coronary deaths, only to eventually succumb to non-cardiovascular deaths. The role of coronary artery disease as a risk factor for death is discussed in further detail later.

In summary, cardiovascular-related deaths comprise the majority of mortality events in HFPEF patients, with greater predominance seen in RCTs compared to epidemiologic studies. Among cardiovascular deaths, sudden death and heart failure death are the leading cardiac MODs in HFPEF clinical trials. Compared to HFREF, the proportions

Table 2. Distribution of deaths in studies with both HFPEF and HFREF

	HFPEF					HFREF				
	Henkel *et al.*[26]	Adabag *et al.*[29]	JCARE-CARD[31]	CHARM[27]	DIG[8, 54]	Henkel *et al.*[26]	Adabag *et al.*[29]	JCARE-CARD[31]	CHARM[27]	DIG[54, 55]
Total Deaths (N)	476	411	169	481	231	441	817	154	1350	2375
Cardiovascular	51	39	58	71	70	64	60	68	83	80
Sudden Cardiac Death	NR	11	11	28	NR	NR	24	23	38	NR
Heart Failure Death	NR	6	35	21	28	NR	6	37	27	35
Coronary Heart Death	29	NR	10	4.4	NR	43	NR	9	6.7	NR
Stroke	NR	NR	4	6.9	NR	NR	NR	3	4.1	NR
Cardiovascular Procedure	NR	NR	0	2.7	NR	NR	NR	1	1.6	NR
Other Cardiac	NR	NR	1	7.3	35	NR	NR	1	5.5	40
Other Vascular	NR	NR	2	NR	7	NR	NR	1	NR	4
Non-Cardiovascular	49	61	28	29	24	36	40	18	17	15
Unknown	0	0	14	0	6	0	0	14	0	5

NR – Not Reported.
All proportions are reported as % of total death.

of cardiovascular deaths, sudden death and heart failure deaths are lower in HFPEF. Conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFPEF than HFREF, particularly in epidemiologic studies, where this difference appears to be primarily related to fewer coronary heart deaths in HFPEF.

WHAT ARE THE RISK FACTORS FOR DEATH IN HFPEF?

Multiple variables are associated with survival in HFPEF. Key risk factors include age, gender, body mass index, burden of comorbidities and coronary artery disease.

Age

Increasing age is associated with higher mortality in HFPEF,32in a variety of clinical settings.13, 33Increasing age is also associated with higher burden of cardiovascular comorbidities in HFPEF (ischemic heart disease, hypertension, diabetes and atrial fibrillation), at least up to the seventh decade.34While age-associated comorbidites confound the risk of death in HFPEF, age alone remains independently predictive of

mortality.29, 35The TIME-CHF study, which included the oldest cohort of HFPEF to date (mean age 80 years), showed that the increase in mortality with age applies even to those ≥75 years compared to those 60-74 years of age.19 This study further showed that MODs were similar in the 2 age groups, which goes against the perception that greater age-associated non-cardiac comorbidity burden may lead to more non-cardiac deaths in the very elderly.

Sex

Women have consistently been shown to have better survival than men with HFPEF. This advantage is observed in both epidemiologic studies36and RCTs,37, 38 all of which analysed long-term follow-up data for at least 2 years. Interestingly, short-term survival odds appear to be non-discriminatory between the sexes, as demonstrated in the Get With The Guidelines-Heart Failure multi-centered registry.39This study found similar risks of in-hospital mortality in both sexes, and extends previous findings of similar risks in short-term outcomes for both groups up till 6 months, after which women displayed better survival probablities.40Although it has been postulated that the premise for better survival in women is due to a lower proportion of heart failure with ischemic origins or a higher LVEF in this group, a recent study comprising of a larger HFPEF population has shown no interaction between LVEF or heart failure etiology with outcomes.38In the large I-PRESERVE HFPEF trial (60% women),41 the lower risk of death in women was shown to apply not only to all-cause deaths, but also to both cardiovascular and non-cardiovascular deaths. The latter runs contrary to the hypothesis that women with HFPEF, being older than men with HFPEF, may have more non-cardiac comorbidities contributing to more non-cardiovascular deaths. Most notably, the I-PRESERVE study showed that the association between sex and mortality risk was significantly modified by 4 risk factors (atrial fibrillation, renal dysfunction, angina, New York Heart Association [NYHA] status), such that the sex difference was ameliorated in the presence of atrial fibrillation or renal dysfunction, or in the absence of angina or NYHA class ≥3 symptoms.

Obesity

The obesity paradox refers to a U-shape relationship of body mass index (BMI) with mortality, with highest hazards in groups with the lowest and highest BMI. Although earlier studies of BMI in undifferentiated heart failure showed increased risk only with lower BMI,42the U-shape relationship was observed in recent studies of chronic heart failure patients43and specifically, the HFPEF population.44, 45In I-PRESERVE, BMI at extreme quintiles of <23.5kg/m2 and ≥35kg/m2 were associated with increased risk of the primary composite outcome (death or cardiovascular hospitalization), as well as all-cause deaths alone.45 Mortality risk was highest in the lowest BMI quintile. The association between BMI and mortality risk varied with the MOD: heart failure deaths demonstrated the U-shape relationship with BMI, whereas the rates of both sudden death and non-cardiovascular death declined linearly with increasing BMI. Heart failure-related inflammation, stress hormone activation and excessive catabolism leading to muscle wasting may explain the excess heart failure mortality in the lowest BMI group. Greater metabolic reserve and lipoprotein pools to neutralize circulating lipopolysaccharide endotoxins may explain the lower sudden death and non-cardiovascular death in more obese patients, but does not explain the higher heart failure mortality in the severely obese.

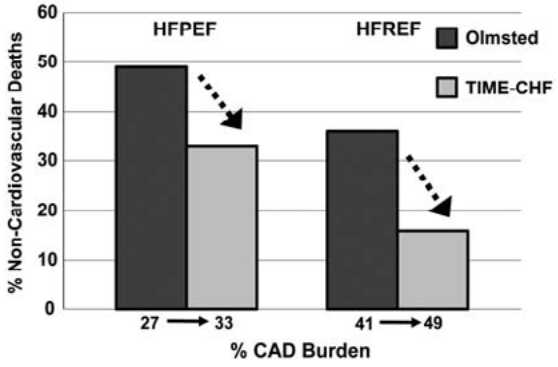

Figure 5. Inverse relationship between prevalence of coronary artery disease and % non-cardiovascular deaths Comparison of baseline burden of coronary artery disease and % of non-cardiovascular related deaths (% total deaths) from similar HF populations (Olmsted26 and TIME-CHF1) shows an inverse relationship regardless of LVEF.

Non-cardiac comorbidities

Since HFPEF is a disease syndrome of the elderly, age-associated non-cardiac comorbidities are highly prevalent in these patients. A greater comorbidity burden, indexed by the Charlson score, is known to be associated with reduced short- and long-term survival in heart failure regardless of LVEF.19, 46Specifically in HFPEF, non-cardiac comorbidities have been shown to be related to increased incidence of future HFPEF,47 reduced functional status,48 and increased risk of hospitalizations.4 In fact, compared to HFREF, non-cardiac comorbidities were found to impact functional status to a greater extent in HFPEF,48 and to potentially account for more non-heart failure hospitalizations in HFPEF than HFREF.49A greater non-cardiac comorbidity burden in HFPEF, particularly in community-based HFPEF, offers a potentially simple explanation for the mortality differences between epidemiologic studies and RCTs, or between HFPEF and HFREF. However, the extent to which non-cardiac comorbidities predict death in HFPEF remains unclear, and non-cardiac comorbidities alone do not explain mortality differences between different heart failure cohorts. For example, in Olmsted County, the burden of non-cardiac comorbidities was similar between HFPEF and HFREF groups, yet % non-cardiovascular deaths was higher in the former.26 Nonetheless, recent mortality risk scores in HFPEF have attempted to quantify the risk associated with non-cardiac factors in HFPEF.32, 50While more research is needed to fully define this risk, it is clear that attention must be paid to non-cardiac comorbidities in the optimal management of HFPEF.

Coronary artery disease

Coronary artery disease plays an important role in the pathophysiology of HFPEF,51 and coronary heart deaths constitute the chief cardiovascular COD in HFPEF from epidemiologic studies.26 Whereas differences in prevalence of non-cardiac comorbidities do not fully account for the contrasting burden of non-cardiovascular deaths between cohorts, the extent of coronary artery disease appears to be inversely related to the the burden of non-cardiovascular deaths in different heart failure cohorts. Using the Olmsted County community-based cohortand the RCT population from TIME-CHFas representative studies investigating

COD in both HFPEF and HFREF, a lower baseline proportion of coronary artery disease was related to a higher proportion of non-cardiovascular deaths, in both study designs and HF groups (Figure 5).19, 26 A potential explanation for these observations is that patients with HFPEF "escape" coronary heart deaths, only to subsequently die from their non-cardiac comorbidities. Alternatively, patients with coronary artery disease may have been more likely to "transition" to HFREF following their myocardial infarctions, thus enriching the HFREF population eventually with more coronary heart deaths. Indeed, a recent study of longitudinal changes in LVEF over time in patients with heart failure showed that coronary artery disease was a major determinant of change in LVEF: over 5 years, ~39% of HFPEF patients transitioned to HFREF (LVEF<50%), whereas a similar % of HFREF transitioned to HFPEF (LVEF≥50%).52 The presence of coronary artery disease was associated with greater reduction of LVEF in HFPEF, and conversely, the absence of coronary artery disease was associated with a greater improvement of LVEF in HFREF.

CONCLUSION

Our review of how patients with HFPEF die provides the following insights: The mortality burden of HFPEF is substantial, ranging from 10-30% annually, and higher in epidemiologic studies than clinical trials. Mortality rates compared to HFREF appear strongly influenced by the type of study, but are clearly elevated compared to age- and comorbidity-matched controls without heart failure. The majority of deaths in HFPEF are cardiovascular deaths, comprising 51-60% of deaths in epidemiologic studies, and ~70% in clinical trials. Among cardiovascular deaths, sudden death and heart failure death are the leading cardiac modes of death in HFPEF clinical trials. Compared to HFREF, the proportions of cardiovascular deaths, sudden death and heart failure deaths are lower in HFPEF. Conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFPEF than HFREF, particularly in epidemiologic studies, where this difference may be related to fewer coronary heart deaths in HFPEF. Other key mortality risk factors include age, gender, body mass index, and burden of comorbidities. These prior studies provide some guidance for better

prediction of response to therapy in designing clinical trials, but also highlight the urgent need for more consistent reporting of COD/MOD in future studies.

Funding: CSPL is supported by a Clinician Scientist Award from the National Medical Research Council.

Conflict of interest: None

REFERENCES

1. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, Kruger A, Kutty R, Lanas F, Lisheng L, Wei L, Lopez-Jaramillo P, Oguz A, Rahman O, Swidan H, Yusoff K, Zatonski W, Rosengren A, Teo KK. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (The Pure Study): A prospective epidemiological survey. Lancet. 2011;378:1231-1243
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251-259
3. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-69.
4. Senni M, Redfield MM. Heart failure with preserved systolic function. A different natural history? J Am Coll Cardiol. 2001;38(5):1277-82.
5. Satomura H, Wada H, Sakakura K, Kubo N, Ikeda N, Sugawara Y, Ako J, Momomura S. Congestive heart failure in the elderly: comparison between reduced ejection fraction and preserved ejection fraction. J Cardiol. 2012;59(2):215-9.
6. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004;43(3):317-27.
7. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. Eur Heart J. 2006;27(19):2338-45.
8. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Jr., Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: The ancillary digitalis investigation group trial. Circulation. 2006;114(5):397-403.

9. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456-67.
10. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362(9386):777-81.
11. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J. 2012;33(14):1750-7.
12. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007;50(8):768-77.
13. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126(1):65-75.
14. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, Kato N, Takeshita A, Tsutsui H. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J. 2009;73(10):1893-900.
15. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006;355(3):260-9.
16. Lewis BS, Shotan A, Gottlieb S, Behar S, Halon DA, Boyko V, Leor J, Grossman E, Zimlichman R, Porath A, Mittelman M, Caspi A, Garty M. Late mortality and determinants in patients with heart failure and preserved systolic left ventricular function: the Israel Nationwide Heart Failure Survey. Isr Med Assoc J. 2007;9(4):234-8.
17. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. JAMA. 2006;296(18):2209-16.
18. Varadarajan P, Pai RG. Prognosis of congestive heart failure in patients with normal versus reduced ejection fractions: results from a cohort of 2,258 hospitalized patients. J Card Fail. 2003;9(2):107-12.
19. Rickenbacher P, Pfisterer M, Burkard T, Kiowski W, Follath F, Burckhardt D, Schindler R, Brunner-La Rocca HP. Why and how do elderly patients

with heart failure die? Insights from the TIME-CHF study. Eur J Heart Fail. 2012;14(11):1218-29.

20. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from “diastolic heart failure” or from misdiagnosis? A prospective descriptive study. BMJ. 2000;321(7255):215-8.
21. Packer M. Can brain natriuretic peptide be used to guide the management of patients with heart failure and a preserved ejection fraction? The wrong way to identify new treatments for a nonexistent disease. Circ Heart Fail. 2011;4(5):538-40.
22. Van Veldhuisen DJ, McMurray JJ. Pharmacological treatment of heart failure with preserved ejection fraction: a glimpse of light at the end of the tunnel? Eur J Heart Fail. 2013;15(1):5-8.
23. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What Have We Learned About Patients With Heart Failure and Preserved Ejection Fraction From DIG-PEF, CHARM-Preserved, and I-PRESERVE? J Am Coll Cardiol. 2012;60(23):2349-56.
24. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, Redfield MM. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail. 2012;5(6):710-9.
25. Narang R, Cleland JG, Erhardt L, Ball SG, Coats AJ, Cowley AJ, Dargie HJ, Hall AS, Hampton JR, Poole-Wilson PA. Mode of death in chronic heart failure. A request and proposition for more accurate classification. Eur Heart J. 1996;17(9):1390-403.
26. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail. 2008;1(2):91-7.
27. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pocock S, Pfeffer MA. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation. 2004;110(15):2180-3.
28. Lee DS, Gona P, Albano I, Larson MG, Benjamin EJ, Levy D, Kannel WB, Vasan RS. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. Circ Heart Fail. 2011;4(1):36-43.
29. Adabag S, Smith LG, Anand IS, Berger AK, Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. J Card Fail. 2012;18(10):749-54.
30. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE. Mode of death in

patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. Circulation. 2010;121(12):1393-405.

31. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, Yamada S, Yokoshiki H, Tsutsui H. Mode of death in patients with heart failure and reduced vs. preserved ejection fraction: Report from the registry of hospitalized heart failure patients. Circ J. 2012;76(7):1662-9.
32. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. On behalf of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC). Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J;doi:10.1093/eurheartj/ehs337. Published online ahead of print 24th October 2012.
33. Gustafsson F, Torp-Pedersen C, Seibaek M, Burchardt H, Kober L, group Ds. Effect of age on short and long-term mortality in patients admitted to hospital with congestive heart failure. Eur Heart J. 2004;25(19):1711-7.
34. Mogensen UM, Ersboll M, Andersen M, Andersson C, Hassager C, Torp-Pedersen C, Gustafsson F, Kober L. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. Eur J Heart Fail. 2011;13(11):1216-23.
35. Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy F, Peltier M, Slama M, Massy Z. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J. 2008;29(3):339-47.
36. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. J Card Fail. 2004;10(5):374-9.
37. Deswal A, Bozkurt B. Comparison of morbidity in women versus men with heart failure and preserved ejection fraction. Am J Cardiol. 2006;97(8):1228-31.
38. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Pina IL, Granger CB, Ostergren J, Michelson EL, Solomon SD, Pocock S, Yusuf S, Swedberg K, Pfeffer MA. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation. 2007;115(24):3111-20.
39. Hsich EM, Grau-Sepulveda MV, Hernandez AF, Peterson ED, Schwamm LH, Bhatt DL, Fonarow GC. Sex differences in in-hospital mortality in acute decompensated heart failure with reduced and preserved ejection fraction. Am Heart J. 2012;163(3):430-7, 437 e1-3.
40. Vaccarino V, Chen YT, Wang Y, Radford MJ, Krumholz HM. Sex differences in the clinical care and outcomes of congestive heart failure in the elderly. Am Heart J. 1999;138(5 Pt 1):835-42.
41. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M,

McKelvie RS, McMurray JJ, Zile MR, Massie BM, Kitzman DW. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail. 2012;5(5):571-8.

42. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J. 2008;156(1):13-22.
43. Schwartzenberg S, Benderly M, Malnick S, George J, Goland S. The “obesity paradox”: does it persist among Israeli patients with decompensated heart failure? A subanalysis of the Heart Failure Survey in Israel (HFSIS). J Card Fail. 2012;18(1):62-7.
44. Kapoor JR, Heidenreich PA. Obesity and survival in patients with heart failure and preserved systolic function: a U-shaped relationship. Am Heart J. 2010;159(1):75-80.
45. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail. 2011;4(3):324-31.
46. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. Arch Intern Med. 2002;162(15):1689-94.
47. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation. 2011;124(1):24-30.
48. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Dungen HD, Scheffold T, Zugck C, Maisch B, Regitz-Zagrosek V, Hasenfuss G, Pieske BM, Wachter R. Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. Clin Res Cardiol. 2011;100(9):755-64.
49. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012;59(11):998-1005.
50. Senni M, Parrella P, De Maria R, Cottini C, Bohm M, Ponikowski P, Filippatos G, Tribouilloy C, Di Lenarda A, Oliva F, Pulignano G, Cicoira M, Nodari S, Porcu M, Cioffi G, Gabrielli D, Parodi O, Ferrazzi P, Gavazzi A. Predicting heart failure outcome from cardiac and comorbid conditions: The 3C-HF score. Int J Cardiol; doi:10.1016/j.ijcard.2011.10.071. Published online

ahead of print 28th November 2011.

51. Choudhury L, Gheorghiade M, Bonow RO. Coronary artery disease in patients with heart failure and preserved systolic function. Am J Cardiol. 2002;89(6):719-22.
52. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. Circ Heart Fail. 2012;5(6):720-6.
53. Perez de Isla L, Canadas V, Contreras L, Almeria C, Rodrigo JL, Aubele AL, Mataix L, Herrera D, Serra V, Zamorano J. Diastolic heart failure in the elderly: in-hospital and long-term outcome after the first episode. Int J Cardiol. 2009;134(2):265-70.
54. Maeder MT, Kaye DM. Differential impact of heart rate and blood pressure on outcome in patients with heart failure with reduced versus preserved left ventricular ejection fraction. Int J Cardiol. 2012;155(2):249-56.
55. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336(8):525-33.

Chapter 3

Pathophysiology of heart failure with preserved ejection fraction

3.1. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota.

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ABSTRACT

Background: Mechanisms purported to contribute to the pathophysiology of heart failure (HF) with normal ejection fraction (HFnlEF) include diastolic dysfunction, vascular and ventricular (LV) systolic stiffening, and volume expansion. We characterized LV volume, effective arterial (Ea), LV end-systolic (Ees) and LV diastolic elastance and relaxation non-invasively in consecutive HFnlEF patients and appropriate controls in the community.

Methods and Results: Olmsted County, Minnesota residents without CV disease (CON; n=617); with hypertension but no HF (HTN; n=719); or with HFnlEF (n=244) were prospectively enrolled . End-diastolic volume index (EDVI) was determined by echo-Doppler. Ees was determined using blood pressure, stroke volume, EF, timing intervals and estimated normalized ventricular elastance at end-diastole. Tissue Doppler e' velocity was used to estimate the time constant of relaxation (τ). EDV and Doppler-derived end diastolic pressure (EDP) were used to derive the diastolic curve fitting (α) and stiffness (β) constants (EDP = αEDVβ). Comparisons were adjusted for age, sex and body size. HFnlEF patients had more severe renal dysfunction, yet smaller EDVI and cardiac output and increased EDP compared to both HTN and CON. Ea and Ees were similarly increased in HTN and HFnlEF compared to CON. In contrast, HFnlEF patients had more impaired relaxation and increased diastolic stiffness compared with either control group.

Conclusions: Based on these cross-sectional observations, we speculate that progression of diastolic dysfunction plays a key role in the development of HF symptoms in persons with hypertensive heart disease

INTRODUCTION

Heart failure (HF) with normal ejection fraction (EF; HFnlEF) is a major public health problem of increasing prevalence.1 In contrast to the improvements in survival observed in patients with HF and reduced EF, mortality for patients with HFnlEF has remained stable, emphasizing the lack of proven therapies.1 An important barrier to advances in therapy is relative uncertainty regarding the fundamental pathophysiologic mechanisms. Left ventricular (LV) diastolic dysfunction (impaired relaxation and increased passive diastolic stiffness), increased systolic ventricular-vascular stiffening, and cardiac volume overload have been implicated in previous seminal studies.2-9 While well designed, these important studies were small, with both control and HFnlEF cohorts subject to potential limitations in regards to selection and referral bias, and in some instances, with populations pre-selected for features of cardiac remodeling or dysfunction. The relative incidence of each putative mechanism remains to be defined in a large, prospectively enrolled, control and heart failure populations recruited from the same community and studied in a comprehensive and uniform manner.

In this study of Olmsted County, Minnesota, residents, we employed previously validated non-invasive methods to assess LV volume,10 end-systolic LV11 and effective arterial stiffness (elastance),12 LV relaxation13,14 and diastolic elastance15 in order to compare cardiac structure and ventricular-vascular function in consecutive patients with HFnlEF to those observed in randomly selected persons without cardiovascular disease, or with hypertension, but no HF. We hypothesized that more advanced diastolic dysfunction and systolic ventricular-vascular stiffening distinguish HFnlEF from disease-free and hypertensive controls without HF in this community.

METHODS

Study setting

The unique aspects of Olmsted County, Minnesota, favoring population-based research have been previously described.16 The study was approved by the Mayo Institutional Review Board. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Identification of patients and study procedures

Subject groups were: 1. Non-obese controls without cardiovascular disease (CON); 2. Subjects with hypertension but without HF (HTN); and 3. Patients with HFnlEF. To recruit the first two groups, a random sample of the population ≥ 45 years old was prospectively identified and evaluated as previously described.16 Data from this study has previously been published, but these subsets and many of the indices presented here have not. Medical records were reviewed by trained nurse abstractors using established criteria for hypertension and HF. Clinical diagnoses of coronary artery disease, diabetes mellitus, valvular heart disease, cardiomyopathy, atrial fibrillation and transient ischemic attack or stroke were recorded. Each participant had measurement of cuff blood pressure, height and weight, with calculation of body mass index (BMI) and body surface area (BSA). Echocardiographic assessment of EF was performed by M-mode, quantitative and semiquantitative two-dimensional (2D) methods. Subjects with EF <50% were excluded. Of 2042 participants, 617 had none of the above validated or suspected cardiovascular diagnoses, a systolic pressure <140 mmHg at the time of echocardiography and a BMI <30 kg/m2, thus constituting the CON group. Subjects with hypertension but no HF (n=719) constituted the HTN group. The HFnlEF group was prospectively identified in an Olmsted County HF surveillance study by real-time interrogation of electronic medical records using natural language processing techniques.17 Briefly, all in- and out-patient electronic notes were searched (most within 24 hours of presentation) using a wide range of terms indicative of HF, enabling rapid identification of all potential cases of HF with a diagnostic sensitivity of 100%.17 The final diagnosis of HF was validated by trained nurse abstractors using the Framingham criteria. Of 811 HF patients identified between 9/10/2003 and 8/24/2005, 570 (70%) consented for participation and 516 (91%) underwent echocardiography within a median (25th, 75th percentile) of one (1,5) day of diagnosis. Of these, 276 patients had EF ≥50%. Hemodynamically significant valve disease was detected on Doppler echocardiography in 32 (11.6%) patients who were excluded. The remaining 244 patients made up the HFnlEF group. Reflecting the ethnic composition of the community, subjects were almost exclusively Caucasian.

Plasma brain natriuretic peptide (BNP) was determined by immunoradiometric assay (nonextracted) using antibody to human BNP (Shionogi Co. Ltd., Tokyo, Japan). Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease Study equation. All echocardiograms were performed by registered diagnostic cardiac sonographers using standardized instruments and techniques16 and were reviewed by a cardiologist (CSL, MMR).

Assessment of cardiac volume

LV volume was determined in each subject by three methods. The Teichholz method18 used short-axis LV dimension measured from 2D or M-mode images. This was available in 532 (86%) CON, 551 (77%) HTN and 222 (91%) HFnlEF subjects. In 73 subjects, LV short-axis dimension was measured from both 2D and M-mode images and correlated well ($r=0.73$, $p<0.001$) with no systematic error (using Bland-Altman analysis, mean difference ± SD = 0.79 ± 4.2 mm) and no relationship between mean difference and the average of the two methods ($r=0.02$, $p=0.85$). LV volume calculated by the area-length formula10 used both long- and short-axis LV dimensions. This was available in 496 (80%) CON, 492 (68%) HTN and 188 (77%) HFnlEF subjects. LV volume was also calculated independent of geometric assumptions by dividing stroke volume (SV; using left ventricular outflow tract dimension and pulsed wave Doppler velocity profile) by EF. This was available in 611 (99%) CON, 697 (97%) HTN and 223 (91%) HFnlEF subjects. Left atrial volume (LAV) was calculated by the ellipse formula.19 LV mass and relative wall thickness (RWT) were calculated by standard methods.10 Measurements were indexed (I) to BSA where appropriate. LV hypertrophy (LVH) was defined as LV mass index >95 g/m2 (females) or >115 g/m2 (males) and LV geometry classified as normal, concentric remodeling, concentric LVH or eccentric LVH.10

Determination of vascular function

Effective arterial elastance (Ea) was estimated as end-systolic pressure (ESP)/ SV.12 ESP was estimated as systolic pressure*0.9, as previously validated.11,12 Total arterial compliance (Ca) was estimated by SV/pulse pressure ratio20 and systemic vascular resistance index (SVRI) by [(mean arterial pressure/cardiac index)*80].

Determination of LV end-systolic elastance

The modified single-beat method was used to estimate end-systolic elastance (Ees) from arm-cuff pressures, SV, pre-ejection and total systolic periods determined on continuous wave Doppler of aortic flow, EF, and an estimated normalized ventricular elastance at arterial end-diastole, as previously validated11,21 and employed in recent studies.4,22,23

Determination of early LV relaxation velocity and filling pressures

The medial mitral annular early diastolic velocity (e') was determined by spectral tissue Doppler imaging using standard methods. The e' velocity is relatively preload-independent and inversely related to the time constant of isovolumic relaxation τ, which was derived by the formula [$\tau = (14.70 - 100e') / 0.15$].13,14 Early transmitral flow velocity (E) was measured by pulse wave Doppler. End-diastolic pressure (EDP) was estimated as: [$EDP = 11.96 + 0.596*E/e'$] as previously determined from Doppler and invasive EDP measurements at our institution.13

Determination of LV diastolic stiffness

The recently developed and validated single-beat approach proposed by Klotz et al was used to characterize the end-diastolic pressure-volume relationship (EDPVR, where $EDP = \alpha EDV^{\beta}$; α = curve fitting constant and ß = diastolic stiffness constant).15 Based on the premise that volume-normalized EDPVRs share a common shape, this method allows the estimation of α and ß, and hence the entire EDPVR, from a single pressure-volume point. Measured EDP and EDV were used to derive α and ß in each subject. A modified method was used when EDP >28 mmHg to address the recognized mathematical limitations of the original equations (see Appendix). In order to account for covariance in α and ß,24 both of which are indicative of the shape and position of the EDPVR, derived α and ß in each subject were used to predict the EDV at a common EDP of 20 mmHg (EDV20). Comparison of EDV20 indexed to BSA (EDVI20) was then used as a comparison of overall diastolic stiffness between groups.

Statistical methods

Categorical variables were compared using the Pearson Chi-square test. Continuous variables were log transformed as necessary and compared between groups using one-way ANOVA with Bonferroni correction for multiple unadjusted comparisons. Regression analysis was used to adjust for age and sex and BSA or the presence of other diseases in group comparisons, where the dependent variable was the normally distributed continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest, and factors entered into the model were age, sex, BSA, and group (dummy variable). Any interaction between these variables was also evaluated and accounted for as appropriate. All analyses were two-sided and significance was judged at $p<0.05$.

RESULTS

Subject characteristics

HFnlEF patients were older, more obese, had higher prevalence of coronary artery disease and diabetes and had lower GFR than HTN or CON (Table 1).

Table 1: Subject characteristics

	CON (n=617)	**HTN** (n=719)	**HFnlEF** (n=244)
Age (range), years	57 (45-96)	66 (46-91)*	76 (22-99) *†
Males, %	45	44	45
Height, cm	169±10	167±10*	165±13*
Weight, kg	73±13	84±19*	86±25*
Body surface area, m^2	1.85±0.21	1.96±0.26*	1.97±0.31*
Body mass index, kg/m^2	25.4±2.7	29.8±5.9*	32.2±20.7*†
Hypertension, %	0	100*	96*
Coronary artery disease, %	0	16*	53*†
Diabetes mellitus, %	0	11*	37*†
Glomerular filtration rate, ml/min/1.73m^2	74.4±14.1	74.7±37.0	64.3±28.1*†
BNP (Shionogi), pg/ml	20.0±40.3	30.5±45.2*	260.7±330.2*†
Log BNP (Shionogi, pg/ml)	1.06±0.41	1.23±0.46*	2.15±0.55*†
Ejection fraction, %	63±5	65±6	62±6*†
Heart rate, bpm	65±10	67±12	71±15*†
Systolic blood pressure, mmHg	118±12	143±21*	132±23*†
Diastolic blood pressure, mmHg	70±8	76±11*	67±14†
Pulse pressure, mmHg	48±11	67±18*	65±20*

Data are mean SD unless otherwise stated. Unadjusted analysis. * $p<0.05$ vs CON; † $p<0.05$ vs HTN

BSA, body surface area; BNP, B-type natriuretic peptide

LV structure

Adjusting for age and sex, EDVI in HFnlEF was similar (Area-length) or smaller (Teichholz and Doppler) compared to CON, and smaller (by all 3 methods) compared to HTN (Table 2). Adjusting for age and sex, SVI in HFnlEF was smaller compared to CON or HTN, while cardiac index in HFnlEF was similar to that in CON but reduced compared to HTN. Adjusting for age and sex, LV mass index, RWT and LV mass to volume ratio were increased in HFnlEF and HTN compared to CON, but these parameters were similar in HFnlEF and HTN. The %LVH was greater in HTN and HFnlEF than in CON but similar in HFnlEF and HTN. LV geometry patterns varied considerably in both control populations and in HFnlEF. While HFnlEF patients had more concentric LVH and less normal geometry compared to CON, these patterns were not significantly different compared to HTN after adjusting for age.

Vascular function

Adjusting for age, sex and BSA where appropriate, Ea, SVRI and pulse pressure were increased while Ca was decreased in HFnlEF and HTN compared to CON, but all these parameters were similar in HFnlEF and HTN (Table 2). Unadjusted comparisons gave similar results.

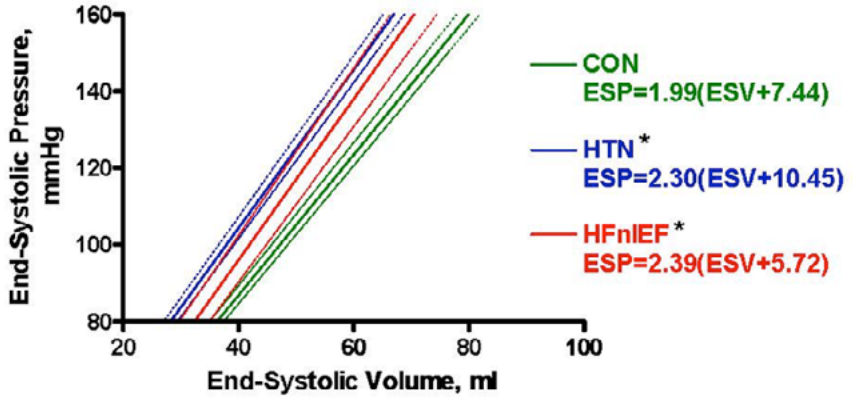

Figure 1: Schematic of group-averaged end-systolic pressure-volume relationship (ESPVR), where ESP = Ees(ESV-V_0) (Ees = end-systolic elastance; V_0 = volume intercept). Solid lines represent the mean ESPVR and dotted lines the 95% confidence intervals for each group. For comparison of Ees (slope) between groups, *p<0.05 vs CON.

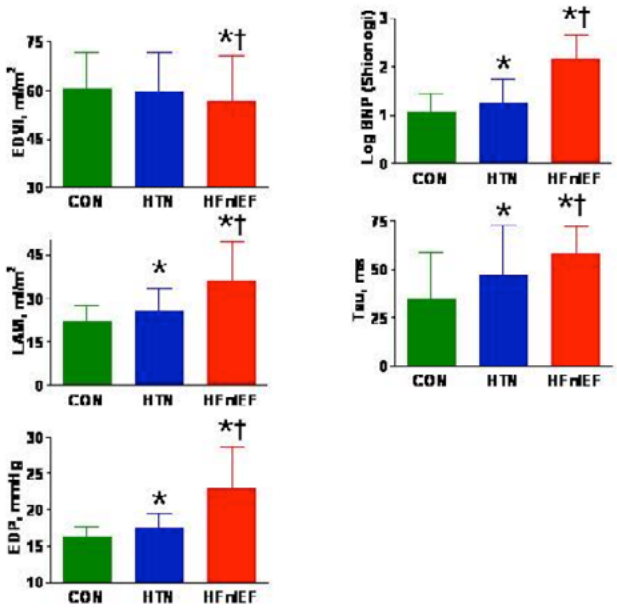

Figure 2: Bar graphs of indexed end-diastolic volume (EDVI), indexed left atrial volume (LAVI), end-diastolic pressure (EDP), plasma brain natriuretic peptide (BNP) and derived tau by subject group. Data are mean ± SD; *p<0.05 vs CON; † p<0.05 vs HTN.

LV Systolic stiffness

Adjusting for age, sex and BSA, Ees was increased in HFnlEF and HTN compared to CON but was similar in HFnlEF and HTN (Table 2). Similar results were observed in unadjusted comparisons and after normalizing Ees for LV mass (Ees*LV mass) and EDV (Ees*EDV) (and adjusting for age and sex), suggesting that the differences in Ees could not be solely attributed to differences in chamber size. Systolic vascular-ventricular coupling ratio (Ea/Ees) was preserved across groups. Predicted ESPVR equations derived from group-averaged data are given in Figure 1.

Estimated LV filling pressures

EDP was higher in HFnlEF compared to both CON and HTN (Figure 2), with corroborating evidence of elevated filling pressures provided by plasma BNP and LAVI measurements.

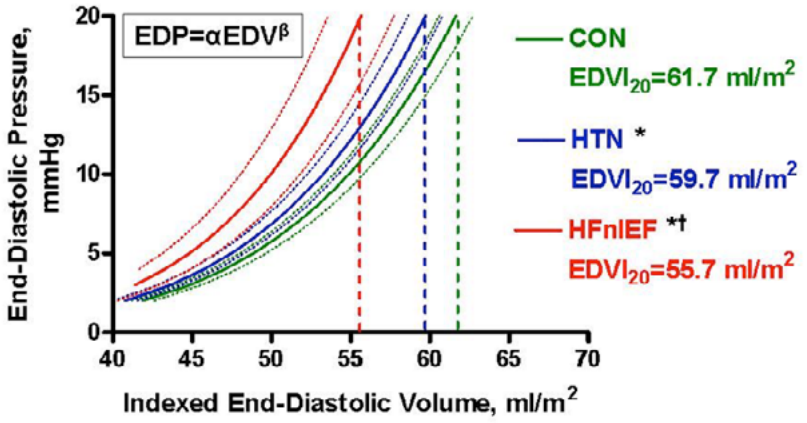

Figure 3: Schematic of group-averaged end-diastolic pressure-volume relationship (EDPVR), where EDP = αEDVβ (α = curve fitting constant; β = diastolic stiffness constant). Solid lines represent the mean EDPVR and dotted lines the 95% confidence intervals for each group. For comparison of indexed EDV at a common EDP of 20 mmHg (EDVI20) between groups, *p<0.05 vs CON; † p<0.05 vs HTN.

LV diastolic function

In both unadjusted and adjusted (adjusting for age, sex and BSA) comparisons, HFnlEF patients had more impaired relaxation (lower e', longer τ) and higher β compared to CON and HTN (Table 2). Adjusting for age and sex and controlling for covariance in α and β, overall diastolic LV stiffness was higher (lower EDVI20) in HFnlEF than in CON or HTN (Table 2). Predicted EDPVR curves derived from group-averaged data are illustrated in Figure 3.

Further analyses

In view of the large age range of subjects (Table 1) and recognizing that unaccounted confounders may be present at the extremes of ages, a sub-analysis of subjects aged 60-95 years was performed and gave similar results (Table 3). Further recognizing potential confounding effects of diabetes and renal function, we adjusted for these in addition to adjusting for age, sex and body size (Table 4). Overall results were similar.

Table 2: Measures of cardiovascular structure and function

		CON (n=617)	HTN (n=719)	HFnlEF (n=244)
LV structure				
EDV, ml	Teichholz	110.6±23.6	113.3±26.1	110.2±32.6
	Area-length	123.2±30.3	125.9±32.9	119.4±39.3†
	Doppler	134.4±31.4	141.1±35.5	132.8±37.7†
EDVI, ml/m^2	Teichholz	60.6±10.9	59.7±12.2	56.4±14.4*†
	Area-length	66.6±12.3	64.9±13.9	60.9±16.1†
	Doppler	72.5±12.9	72.2±15.5	68.1±16.6*†
Stroke volume index, ml/m^2		45.8±7.5	46.3±9.5	42.3±10.0*†
Cardiac index, l/min/m^2		2.94±0.57	3.04±0.70	2.95±0.79†
LV mass, g		164.2±38.8	195.0±53.2*	200.4±67.1*
LV mass index, g/ m^2		88.8±16.3	100.2±22.7*	102.1±29.0*
LV mass/EDV, mg/ml		1.50±0.28	1.75±0.39*	1.85±0.47*
Relative wall thickness		0.38±0.06	0.42±0.07*	0.45±0.10*
% LV hypertrophy		18%	40%*	42%*
% Normal geometry		66	39*	31*
% Concentric remodeling		16	21	27
% Concentric hypertrophy		5	21*	26*
% Eccentric hypertrophy		13	19	16
Vascular function				
Effective arterial elastance (Ea), mmHg/ml		1.30±0.30	1.50±0.41*	1.53±0.43*
Systemic vascular resistance index, dyne.s.cm^{-5}.m^2		2424±521	2703±657*	2588±873*
Arterial compliance, ml/mmHg		1.86±0.58	1.45±0.55*	1.41±0.93*
LV systolic function				
End-systolic elastance (Ees), mmHg/ml		1.99±0.59	2.30±0.80*	2.39±0.87*
Ees*LV mass		319.7±96.4	439.6±163.7*	461.8±209.7*
Ees*EDV		215.5±60.7	256.3±86.3*	254.0±105.3*
Ea/Ees		0.68±0.13	0.68±0.17	0.69±0.22
LV diastolic function				
E, m/s		0.660±0.131	0.671±0.169*	0.979±0.347*†
A, m/s		0.561±0.161	0.722±0.203*	0.848±0.267*†
E/A ratio		1.25±0.38	0.99±0.37*	1.21±0.69*†
Deceleration time, ms		222±33	239±43	208±54*†
e', m/s		0.094±0.035	0.077±0.039*	0.060±0.021*†
τ, ms		35.2±23.4	46.8±26.0*	58.1±14.3*†
E/e' ratio		7.55±2.29	9.43±3.32*	18.43±9.65*†
LV end-diastolic pressure (EDP), mmHg		16.5±1.4	17.6±2.0*	22.9±5.7*†
Diastolic stiffness constant (ß)		5.96±0.06	6.05±0.41*	7.09±3.55*†
$EDVI_{20}$, ml/m^2		61.7±11.4	59.7±11.9*	55.7±14.5*†
EDP/EDV, mmHg/ml		0.16±0.04	0.16±0.05	0.23±0.11*†

Data are mean ± SD; Comparisons adjusted for age and sex, as well as body surface area (BSA) where appropriate; *p<0.05 vs CON; †p<0.05 vs HTN; LV, left ventricular; EDV, end-diastolic volume; I, indexed to BSA

DISCUSSION

This is the largest population-based study to date comparing vascular and ventricular structure and function in a HFnlEF cohort to that observed in healthy and hypertensive control populations without HF. The current study serves to confirm, clarify and extend smaller, seminal studies describing a variety of structural and functional perturbations in

Table 3: Subgroup analysis in subjects aged 60 to 95 years

		CON (n=211)	HTN (n=519)	HFnlEF (n=214)
EDVI, ml/m^2	Teichholz	59.4±12.1	60.0±12.7	56.7±14.2* †
	Area-length	63.7±12.8	64.7±14.0	60.8±15.6†
	Doppler	72.0±13.4	73.4±16.0	68.1±16.6* †
Effective arterial elastance, mmHg/ml		1.35±0.32	1.53±0.43*	1.54±0.43*
End-systolic elastance, mmHg/ml		2.12±0.64	2.37±0.83*	2.42±0.88
$EDVI_{20}$, ml/m^2		60.5±12.8	60.0±12.3	55.7±14.3*†
τ, ms		41.3±27.7	49.1±28.0	59.5±13.1* †

Data are mean SD; Comparisons adjusted for age, sex and body surface area (BSA) where appropriate; *p<0.05 vs CON; p<0.05 vs HTN; EDVI, end-diastolic volume indexed to BSA

Table 4: Analysis adjusting for renal function, diabetes, age, sex and body size

	CON (n=617)	HTN (n=719)	HFnlEF (n=244)
Effective arterial elastance, mmHg/ml	1.30±0.30	1.50±0.41*	1.53±0.43*
End-systolic elastance, mmHg/ml	1.99±0.59	2.30±0.80*	2.39±0.87*
$EDVI_{20}$, ml/m^2	61.7±11.4	59.7±11.9	55.7±14.5*†
τ, ms	35.2±23.4	46.8±26.0*	58.1±14.3*†

Data are mean SD; Comparisons adjusted for glomerular filtration rate, diabetes, age, sex and body surface area (BSA); *p<0.05 vs CON; p<0.05 vs HTN; EDVI, end-diastolic volume indexed to BSA

more select cohorts with HFnlEF. Several findings are noteworthy. The HFnlEF cohort had worse renal function, yet smaller LV volume and cardiac output as compared to hypertensive controls. While LV mass was, on average, increased in HFnlEF as compared to healthy controls, HFnlEF patients did not have more severe LVH than hypertensive controls. Compared to healthy controls, the HFnlEF cohort had increases in both the resistive and pulsatile components of vascular load with proportional increases in LV systolic stiffness. However, these abnormalities were similar to those observed in hypertensive controls without HF. In contrast, diastolic dysfunction (both impairment in relaxation and increases in diastolic stiffness) was more severe in HFnlEF patients as compared to healthy or hypertensive controls.

The current findings are consistent with previous studies which

utilized invasive assessment of LV function in HFnlEF. Liu et al. used conductance catheters with preload reduction (multiple-beat method) in 10 patients with LVH and normal EF (7 with HFnlEF) and found impaired relaxation with increased diastolic stiffness in this group compared to 8 younger, healthy controls.25 All subjects were referred for cardiac catheterization at a tertiary center.25 In a landmark invasive study using a single-beat method, Zile et al. also found more impaired relaxation and higher diastolic stiffness in HFnlEF (n=47). These HFnlEF patients were predominantly male with echocardiographic evidence of LVH recruited at a Veterans Administration Hospital as part of a clinical trial and were compared to 10 healthy age-matched controls.2 In both these studies, the control group had no cardiovascular disease, raising concern as to whether the observed differences were specifically attributable to HFnlEF, or to hypertensive heart disease. Borbely et al. measured chamber and myocyte stiffness in 12 HFnlEF patients and 8 controls, and found increased estimated LV diastolic stiffness in HFnlEF by invasive measurements.26 However, nearly half the HFnlEF and 75% of control patients had previously undergone cardiac transplantation, thus confounding effects of occult rejection or immunosuppression may have influenced the findings.

Other studies employed non-invasive methods to characterize diastolic function.27 Ahmed et al identified 26 patients with LVH and HFnlEF undergoing echocardiography at their tertiary center and showed that these patients had more severe diastolic dysfunction than 39 non-hypertensive controls, 14 hypertensive controls and 23 controls with LVH but no HF.6 The inclusion of hypertensive controls was a strength of this study which focused on HFnlEF patients with LVH.

In the current study, consecutive cases of HFnlEF identified in both the inpatient and outpatient settings, and not pre-selected for any geometric characteristics, were compared to large, randomly-selected and prospectively enrolled control populations from the same community, with all subjects studied in a similar manner and using analyses adjusted for potential effects of age, sex and body size. The current results are consistent with the afore-mentioned studies in that relaxation and passive diastolic stiffness were impaired in HFnlEF compared to disease-free controls. Further, the current data confirm

that compared to hypertensive controls, HFnlEF patients have more severe diastolic dysfunction. While the predominant cardiovascular abnormalities and contributing comorbidities in HFnlEF patients may vary according to a number of demographic parameters, it is noteworthy that the presence of diastolic dysfunction is a consistent finding in HFnlEF patients identified in this community and in the diverse settings included in previous studies.2,5-9,25,26

In contrast, Kawaguchi et al., using either invasive (conductance catheters and multiple-beat model) or non-invasive (single-beat model) measurements, found that relaxation was not significantly different in HFnlEF (n=10) compared to young controls (n=9) and age- and blood pressure-matched controls (n=25), except during stress (isometric handgrip).4 Additionally, although higher EDPs were observed in HFnlEF, this was due to a parallel upward shift of the diastolic pressure-volume curve, rather than to a steeper curve (i.e. β stiffness coefficients were similar), suggesting that exaggerated external forces, rather than increased passive diastolic stiffness was present in HFnlEF. However, the large variability in β observed in the HFnlEF group (range ≈ 0.01 to 0.05 mmHg/ml) may have prevented demonstration of differences in β in the small numbers of subjects enrolled. Importantly, this study showed that HFnlEF patients had increased Ea and Ees, suggesting that vascular and LV systolic stiffening may contribute to the pathophysiology of HFnlEF by exaggerating systolic load and diastolic dysfunction during exercise. These patients were studied over a 14-year period at a referral center, and while predominantly female, the mean age was lower than that observed in most population-based studies. Although we also found that Ea and Ees were increased in HFnlEF compared to healthy controls, these indices were not further increased in HFnlEF compared to hypertensive controls in the current study as well as others.5,6,9 Nonetheless, these data do not exclude a role for increased vascular and LV systolic stiffening in the pathophysiology of HFnlEF, particularly during exercise or other stressors where such changes exaggerate hypertensive responses and induce further, load dependent diastolic dysfunction.

The potential for a subgroup of HFnlEF patients to have LV dilatation and a “high output” form of HF has been reported.3 Maurer et

al. used 3-dimensional and Doppler echocardiography to characterize LV volumes and pressures non-invasively at a tertiary referral center in the New York metropolitan area. Among 35 patients with hypertension and HFnlEF, a subgroup (n=29) of younger, more obese subjects had increased LV volumes associated with increased EDP but no change in Ees or Ea compared to healthy controls. These investigators concluded that many (most in their series) HFnlEF patients may have volume overload, without intrinsic diastolic dysfunction as a mechanism for increased filling pressures. In contrast, our data show that on average, compared to healthy or hypertensive controls, HFnlEF patients have normal or decreased LV volumes respectively. Since ventricular volumes vary with body size, sex and possibly age in persons without cardiovascular disease, we were careful to adjust for these parameters in all volume comparisons. We accounted not only for the short-axis but also for the long-axis LV dimension when calculating volumes. A further Doppler-based method was used to estimate volumes independent of geometric assumptions. All 3 methods gave the consistent picture that ventricular enlargement was not present in the majority of HFnlEF patients despite more impaired renal function in these patients. In fact, stroke volume and cardiac index were lower in HFnlEF than in hypertensive controls. As emphasized previously, however, the current analysis is restricted to group comparisons; as LV volume is a continuous variable with a fairly normal distribution in the HFnlEF population, some patients with HFnlEF will have increased LV volume even though the distribution curve as a whole was not shifted towards larger volumes. Indeed, our findings underscore the variable LV geometric patterns present in HFnlEF.

More recently, Melenovsky et al.9 used non-invasive methods to study 37 HFnlEF patients, 40 hypertensive and 56 non-hypertensive age-, gender- and race-matched controls recruited from an urban setting in Baltimore, Maryland. This population was largely African American, and HFnlEF patients were younger (by a decade) than observed here, more obese, and more predominately female. As in our study, LV volume did not vary significantly among groups, estimated filling pressures were highest in HFnlEF, and both Ees and Ea were similarly increased in hypertensive controls and HFnlEF compared to disease-

free controls. However, both the HFnlEF and hypertensive groups had much more dramatic LVH than we observed, and while estimated LV diastolic pressures were higher in HFnlEF, many parameters displayed substantial overlap, with little disparity between these two groups. Although LV diastolic stiffness was not estimated, the prior study found left atrial enlargement and impaired atrial function in HFnlEF, leading the authors to speculate that impaired atrial function may also play a key role in the transition to HFnlEF among patients with cardiovascular disease. This hypothesis is consistent with clinical studies documenting that new onset atrial fibrillation is a common precipitant of episodes of acutely decompensated HF, regardless of EF.28,29 We too found increased left atrial volume in HFnlEF compared to either control group. Melenovsky et al. further found that total epicardial cardiac volume was highest in HFnlEF patients and speculated that external forces may contribute to elevation of filling pressures.

The variable LV geometry patterns observed in HFnlEF patients in our study is noteworthy and consistent with several2,4,28,30 prior studies, underscoring that despite traditional teaching, concentric LVH or concentric remodeling is not invariably present in HFnlEF. Indeed, there may be important geographic and race-specific differences, with marked concentric LVH being more common in some populations, such as African Americans, as seen in studies where these groups are more prominently represented.9 Finally, the similar RWT and LV mass to volume ratio observed in HTN and HFnlEF suggest that factors other than chamber geometry additionally mediate increased diastolic stiffness in HFnlEF. Changes in the cardiomyocytes themselves26 and/or the extracellular matrix31,32 may mediate diastolic stiffening and represent potential therapeutic targets in the treatment and/or prevention of HFnlEF.

Limitations

Our data are purely observational and cannot prove causality. The more impaired diastolic dysfunction in HFnlEF could be a marker for, rather than a mediator of, progression to HF. Although invasive measurements were not performed, each of the methods employed to characterize pressure-volume relationships was validated against gold-standard invasive techniques.

Future directions

While total vascular load and indirect measures of vascular stiffness were obtained here, further study is needed to evaluate more direct and perhaps regional measures of vascular stiffening, and other assessments of arterial impedance and its impact such as characteristic impedance, wave reflections, and pulse wave velocity. Hemodynamic data obtained during exercise and other stresses may be key in differentiating HFnlEF from hypertensive controls. The study population was mainly white and potential differences in other racial groups should be examined. Finally, the functional significance of different geometric patterns in HFnlEF deserves further study.

Conclusion

In this large, population-based study, HFnlEF patients had reduced LV volumes and cardiac output compared to hypertensive controls despite more renal impairment. While HFnlEF patients displayed vascular and LV systolic stiffening as compared to normal controls, HFnlEF was distinguished from hypertensive heart disease by the presence of more severe diastolic dysfunction, and increased left atrial size. Thus, these data support efforts to ameliorate diastolic dysfunction in order to prevent or treat HFnlEF. While we speculate that progression of diastolic dysfunction plays a key role in the development of HF symptoms in persons with hypertensive heart disease and a normal EF, further studies characterizing potential differential responses to exercise and other stressors may reveal additional pathophysiological mechanisms and therapeutic targets.

Funding sources

Public Health Service (NIH HL63281-4, NIH HL72435-2, and NIH HL55502-7).

REFERENCES

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355:251-9.
2. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004;350:1953-9.
3. Maurer MS, King DL, El-Khoury Rumbarger L, Packer M, Burkhoff D. Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. J Card Fail. 2005;11:177-87.
4. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation. 2003;107:714-20.
5. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation. 2005;111:2306-12.
6. Ahmed SH, Clark LL, Pennington WR, Webb CS, Bonnema DD, Leonardi AH, McClure CD, Spinale FG, Zile MR. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. Circulation. 2006;113:2089-96.
7. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation. 2006;113:296-304.
8. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation. 2006;113:1966-73.
9. Melenovsky V, Borlaug B, Rosen B, Hay I, Ferrucci L, Morell C, Lakatta E, Najjar S, Kass D. Cardiovascular features of heart failure with preserved ejection fraction versus non-failing hypertensive left ventricular hypertrophy in the urban Baltimore community. J Am Coll Card. 2007;49:198-207.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W. Recommendations for chamber quantification. Eur J Echocardiogr. 2006;7:79-108.
11. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol. 2001;38:2028-34.
12. Kelly RP, Ting C-T, Yang T-M, Liu C-P, Maughan WL, Chang M-S, Kass DA.

Effective arterial elastance as index of arterial vascular load in humans. Circulation. 1992;86:513-521.

13. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000;102:1788-94.
14. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. Journal of the American College of Cardiology. 1997;30:474-480.
15. Klotz S, Hay I, Dickstein ML, Yi GH, Wang J, Maurer MS, Kass DA, Burkhoff D. Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. Am J Physiol Heart Circ Physiol. 2006;291:H403-12.
16. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289:194-202.
17. Pakhomov SV, Buntrock J, Chute CG. Prospective recruitment of patients with congestive heart failure using an ad-hoc binary classifier. J Biomed Inform. 2005;38:145-53.
18. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. American Journal of Cardiology. 1976;37:7-11.
19. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. Journal of the American College of Cardiology. 2003;41:1036-43.
20. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol. 1998;274:H500-5.
21. Senzaki H, Chen CH, Kass DA. Single-beat estimation of end-systolic pressure-volume relation in humans. A new method with the potential for noninvasive application. Circulation. 1996;94:2497-506.
22. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation. 2005;112:2254-62.
23. Maurer MS, El Khoury Rumbarger L, King DL. Ventricular volume and length in hypertensive diastolic heart failure. J Am Soc Echocardiogr. 2005;18:1051-7.

24. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol. 2005;289:H501-12.
25. Liu C-P, Ting C-T, Lawrence W, Maughan WL, Chang M-S, Kass DA. Diminished contractile response to increased heart rate in intact human left ventricular hypertrophy: Systolic versus diastolic determinants. Circulation. 1993;88:1893-1906.
26. Borbely A, van der Velden J, Papp Z, Bronzwaer JG, Edes I, Stienen GJ, Paulus WJ. Cardiomyocyte stiffness in diastolic heart failure. Circulation. 2005;111:774-81.
27. Oh JK, Hatle L, Tajik AJ, Little WC. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. J Am Coll Cardiol. 2006;47:500-6.
28. Chen HH, Lainchbury JG, Senni M, Bailey KR, Redfield MM. Diastolic heart failure in the community: clinical profile, natural history, therapy, and impact of proposed diagnostic criteria. J Card Fail. 2002;8:279-87.
29. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation. 2000;101:2118-21.
30. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA. 2002;288:2144-50.
31. Lopez B, Gonzalez A, Querejeta R, Larman M, Diez J. Alterations in the pattern of collagen deposition may contribute to the deterioration of systolic function in hypertensive patients with heart failure. J Am Coll Cardiol. 2006;48:89-96.
32. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, Degroof RC. The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. J Card Fail. 2005;11:191-5.

Appendix

A recognized limitation of the original predictions used in the single-beat EDPVR method[15] was the break down of the equations as measured EDP approached 30mmHg. This limitation was due to the arbitrary choice of V_{30} (estimated EDV at 30mmHg) as a starting point in the original derivation equations for α and ß, which therefore became unstable as measured EDP approached 30mmHg (>28mmHg). This mathematical instability was overcome by simply using an estimate of EDV at a pressure of 15mmHg (V_{15}) instead of V_{30} for cases where measured EDP >28mmHg. V_{15} was derived from the EDV normalized curve in the same fashion as V_{30}[15](Burkoff D, MD, PhD, electronic personal communication, 2006). Similar to the original derivations, α and ß were then calculated by solving the simultaneous equations:

$Pm = \alpha\ Vm^{\beta}$ [Equation 1]

$15 = \alpha\ V_{15}^{\beta}$ [Equation 2]

Where Pm = measured pressure (measured EDP) and Vm = measured volume (measured EDV)

Dividing [1] by [2] and solving for ß:

$\beta = \text{Log}\ (Pm/15)/\text{Log}\ (Vm/V_{15})$

Substituting into [1]:

$\alpha = Pm/Vm^{\{\text{Log}\ (Pm/15)/\text{Log}\ (Vm/V15)\}}$

EDPVR curves derived using V_{15} and V_{30} were well-correlated at multiple parts of the curves.

Chapter 3

Pathophysiology of heart failure with preserved ejection fraction

3.2. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study.

Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. J Am Coll Cardiol. 2009;53:1119-26

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ABSTRACT

Objectives: To define the prevalence, severity and significance of pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF) in the general community.

Background: While HFpEF is known to cause PH, its development is highly variable. Population-based data are lacking, and the relative contribution of pulmonary venous versus pulmonary arterial hypertension to PH in HFpEF is unknown. We hypothesized that PH would be a marker of symptomatic pulmonary congestion, distinguishing HFpEF from preclinical hypertensive heart disease (HTN).

Methods: Population-based study of 244 HFpEF patients (76±13y; 45%male) followed from Doppler echocardiography over 3 years. Controls were 719 adults with HTN without HF (66±10y; 44%male). Pulmonary artery systolic pressure (PASP) was derived from the tricuspid regurgitation velocity and PH defined as PASP>35 mmHg. Pulmonary capillary wedge pressure (PCWP) was estimated from E/e'.

Results: In HFpEF, PH was present in 83% and median (25th, 75th percentile) PASP was 48 (37, 56) mmHg. PASP increased with PCWP ($r=0.21$; $p<0.007$). Adjusting for PCWP, PASP was higher in HFpEF than HTN ($p<0.001$). PASP distinguished HFpEF from HTN with an area under receiver-operating curve of 0.91 ($p<0.001$) and strongly predicted mortality in HFpEF (hazard ratio=1.3 per 10 mmHg; $p<0.001$).

Conclusions: PH is highly prevalent and often severe in HFpEF. While pulmonary venous hypertension contributes to PH, it does not fully account for the severity of PH in HFpEF, suggesting that a component of pulmonary arterial hypertension also contributes. The potent effect of PASP on mortality lends support for therapies aimed at pulmonary arterial hypertension in HFpEF.

INTRODUCTION

Left-sided heart failure (HF) is known to cause pulmonary hypertension (PH)(1), but the development and severity of PH in HF is highly variable, and contributing factors are not fully understood. While initial studies focused on patients with reduced left ventricular ejection fraction (EF) (2), early isolated case reports(3,4) and more recent case series(5-7) have demonstrated that PH can occur in HF with preserved EF (HFpEF). There is now growing appreciation that PH is common and may be severe in elderly patients with HFpEF(8). However, the true prevalence and severity of PH in HFpEF from the general community remain unknown. Previous studies were limited by selection bias, and population-based data have, to date, been lacking.

Common to left ventricular failure regardless of EF, increased left-sided filling pressure leads to pulmonary venous hypertension and post-capillary PH. In the presence of preserved systolic function, the development of pulmonary venous hypertension is associated with the severity of left ventricular diastolic dysfunction, as has been demonstrated in patients with aortic stenosis and normal EF(9). Beyond this post-capillary contribution to PH, a reactive increase in pulmonary arterial tone or intrinsic arterial remodeling can result in a superimposed pre-capillary component of pulmonary arterial hypertension. This has been shown to occur in patients with mitral stenosis(10) and HF with reduced EF(11). In HFpEF without valvular disease, however, the relative contributions of these pre- and post-capillary components to PH are unclear. A population-based approach to discerning the role of PH in HFpEF is to compare hypertensive patients with and without HF from the same community. Since hypertensive heart disease is the most common precursor to HFpEF and since elderly hypertensives without HF often display Doppler-echocardiographic features in common with HFpEF, comparisons between these groups of patients can provide insight into mechanisms mediating the progression from hypertensive heart disease to HFpEF and diagnostic features that distinguish preclinical hypertensive heart disease from overt HFpEF(12-14).

We hypothesized that both pulmonary venous hypertension related to diastolic dysfunction, as well as pulmonary arterial hypertension related to increased arterial tone or vascular remodeling, would contribute to

PH in HFpEF. Further, we hypothesized that PH would be related to the development and severity of clinically significant pulmonary congestion, thus distinguishing HFpEF from preclinical hypertensive heart disease without overt HF. Accordingly, the aims of this population-based study were to measure pulmonary artery systolic pressure (PASP), define the prevalence and severity of PH (PASP>35 mmHg), and assess the association between PASP and pulmonary venous hypertension in patients with a clinical diagnosis of HFpEF compared to hypertensive heart disease without HF from the same community. Finally, we sought to determine if PH was associated with mortality in HFpEF presenting in the community.

METHODS

This study was conducted in Olmsted County, MN, with the approval of the Mayo Foundation Institutional Review Board. All subjects provided written informed consent. While data from these patients have previously been published(14,15), many of the indexes proposed here have not.

Study design and subject groups

In this population-based observational study, subject groups included:

Hypertensive control group (HTN)

A random sample (N=2042; studied between June 1997 and September 2000) of the Olmsted County, MN population aged ≥45 years underwent medical review, echocardiography and spirometry. From this cohort, 719 subjects with a history of hypertension but without HF (all EF≥50%) constituted the HTN group.

HFpEF group

Consecutive HFpEF patients (N=244) were identified (between September 2003 and October 2005) in an Olmsted County, MN HF surveillance study as previously described(14). Both in- and out-patients were identified by real-time interrogation of electronic medical records using natural language processing techniques. All patients underwent medical review and echocardiography. HF diagnosis

was validated using the Framingham criteria and EF≥50% without hemodynamically significant left-sided valve disease was confirmed by echocardiography.

Doppler Echocardiography

All echocardiograms were performed by registered diagnostic cardiac sonographers using standardized instruments and protocols, and interpreted by a blinded echocardiologist (C.S.P.L, M.M.R.). All parameters were measured in triplicate and averaged. In addition to standard M-mode, 2-dimensional and color Doppler imaging, continuous-wave Doppler examination of tricuspid flow, pulsed-wave Doppler examination of mitral inflow and Doppler tissue imaging of the medial mitral annulus were performed in each subject as previously described(14,15).

Determination of PH

Since PASP is equal to right ventricular systolic pressure in the absence of pulmonary stenosis, PASP was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as 4v2, where v is the velocity of the tricuspid regurgitation jet in m/s. Right atrial pressure, estimated based on echocardiographic characteristics of the inferior vena cava and assigned a standardized value(16), was then added to the calculated gradient to give PASP. PH was defined as PASP > 35 mmHg(17). Echocardiographic estimates of PASP obtained in this fashion have been shown to correlate well with invasively measured values on right-heart catheterization with a sensitivity and specificity of 0.79 to 1, and 0.6 to 0.98, respectively for predicting PH(18).

Assessment of left ventricular diastolic function

The ratio of early transmitral flow velocity (E) to early mitral annular (medial) diastolic velocity (e') was used to estimate pulmonary capillary wedge pressure (PCWP) [=11.96+0.596 • E/e'] based on prior Doppler and invasive measurements at our institution(19). This index has also been shown to reliably detect pulmonary venous hypertension

in patients with elevated echo-derived PASP undergoing right heart catheterization(20). Other parameters included left atrial volume as calculated by the ellipse formula, and left ventricular mass, both indexed to body surface area(21).

Spirometry

Spirometry was performed in accordance with recommended techniques(22) and measurements standardized as percentages of predicted normal values(23). Chronic obstructive lung disease (COPD) was defined as either a forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of <70%(24) or the presence of a clinical diagnosis of COPD.

Follow up

HFpEF patients were followed from baseline echocardiography at enrollment to death (all-cause mortality) or last contact, at which time they were censored. Follow up was 100% complete with vital status (March 2008) determined from the Mayo Clinic registration database and the Rochester Epidemiology Project death database, where mortality data on Olmsted County residents are routinely collected by reviewing community medical records, death certificates, and obituary notices(15).

Statistical methods

Groups were compared using Pearson's chi-square test for categorical variables and t-test for normally distributed continuous variables. The association between PASP (log transformed to satisfy normality assumptions) and PCWP was investigated by calculating Pearson's correlation coefficient. Regression analyses were used for adjusted comparisons, where the dependent variable was the normally distributed continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest, while factors entered into the model included age, sex, PCWP, group (dummy variable) and appropriate interaction terms. Receiver operating curve analyses were used to determine the ability of echocardiographic parameters (PASP, E/e', left atrial volume index, relative wall thickness, left ventricular

Table 1: Characteristics of subjects with measurable PASP

	HTN		HFpEF	
	PH absent	**PH present**	**PH absent**	**PH present**
N (% group)	432 (92)	38 (8)	34 (17)	169 (83)
PASP, mmHg	28±4	40±5*	30±3	52±13*
Clinical characteristics				
Age, y	67±10	72±9*	74±11	79±12*
Males, %	40	32	47	41
Height, m	1.66±0.10	1.62±0.08*	1.66±0.10	1.65±0.14
Weight, kg	79.6±16.9	75.3±14.5	84.8±17.9	81.6±23.0
BSA, m^2	1.91±0.23	1.83±0.20	1.97±0.24	1.92±0.29
Body mass index, kg/m^2	28.8±5.5	28.8±5.2	30.9±6.3	29.6±7.2
Systolic blood pressure, mmHg	141±21	153±27*	125±20	134±24*
Diastolic blood pressure, mmHg	75±11	75±11	69±13	67±14
Pulse pressure, mmHg	66±18	78±20*	56±18	67±20*
Heart rate, bpm	65±11	65±13	68±15	71±16
Hypertension, %	100	100	91	97
Atrial fibrillation, %	5	13*	22	31
Coronary artery disease, %	16	21	59	53
Diabetes mellitus, %	10	13	27	34
Chronic kidney disease[a], %	29	43	50	51
Chronic obstructive lung disease[b], %	14	21	29	32
Echocardiographic characteristics				
Ejection fraction, %	65±5	65±7	63±5	62±7
Stroke volume/BSA, ml/m^2	46.8±9.3	48.9±10.5	42.7±10.3	43.2±9.8
Cardiac index, $l/min/m^2$	3.0±0.7	3.1±0.8	2.8±0.7	3.0±0.8
LV mass/BSA, g/m^2	99.6±22.4	107.4±31.0	99.7±27.2	103.3±30.1
Relative wall thickness	0.42±0.07	0.42±0.08	0.46±0.11	0.45±0.09
LV end-diastolic volume/BSA, ml/m^2	59.2±12.2	60.7±11.1	54.5±11.4	57.4±15.0
E/e' ratio	9.3±3.3	12.8±4.7*	15.7±9.8	19.6±9.6*
PCWP, mmHg	18±2	20 ±3*	21±6	24±6*
Left atrial volume/BSA, ml/m^2	26.2±7.8	32.7±8.5*	32.1±11.4	38.1±14.3*

Data are mean ±SD

[a]Glomerular filtration rate ≤60 ml/min/1.73m2 {K/DOQI clinical practice guidelines; National Kidney Foundation's web site at www.kidney.org/professionals/kdoqi/guidelines.cfm}

[b]FEV1/FVC <70%(24) or clinical diagnosis

*p<0.05 vs PH absent

PH, pulmonary hypertension; PASP, pulmonary artery systolic pressure; BSA, body surface area; LV, left ventricular; PCWP, pulmonary capillary wedge pressure

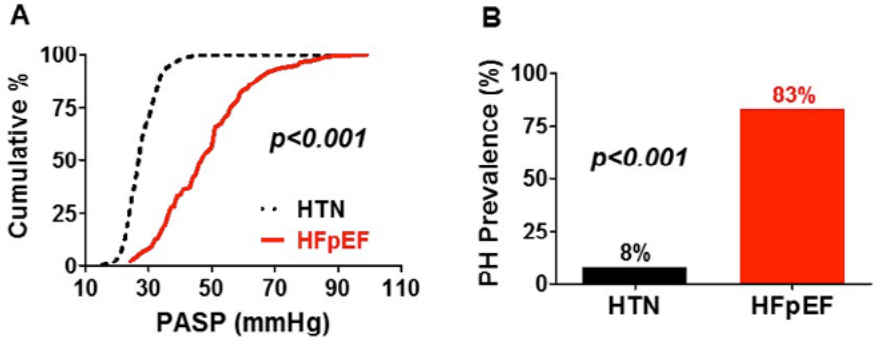


Figure 1: Cumulative frequency distribution of pulmonary artery systolic pressure and prevalence of pulmonary hypertension by subject group In patients with heart failure and preserved ejection fraction (HFpEF, in red), the cumulative frequency distribution of pulmonary artery systolic pressure (PASP) was shifted towards higher pressures (A), while the prevalence of pulmonary hypertension (PH) was markedly increased (B), compared to subjects with hypertension (HTN, in black) without heart failure in the community.

mass index) to distinguish HFpEF from HTN. The optimal cutoff value for each parameter was defined as the value giving the largest area under curve (AUC) for the parameter. The derived mean±standard error AUC for each parameter was compared to that of PASP using t tests as well as paired analyses by the method of Delong (25), with Bonferroni correction to control for multiple comparisons. The effect of PH on survival was assessed by Kaplan-Meier analysis. The association of PASP with mortality was assessed by Cox regression analysis, before and after adjusting for age and other echocardiographic parameters. All analyses were two-sided, and significance was judged at $p<0.05$.

RESULTS

TR jets were analyzable in 470 (65%) of HTN and 203 (83%) of HFpEF. Compared to patients in whom TR jets could not be analyzed, those with analyzable TR jets were older (64±10 vs 70±12 years; $p<0.001$), more often female (46 vs 60%; $p<0.001$), had smaller body size (2.08±0.28 vs 1.91±0.25 m2, $p<0.001$), were more likely to have coronary artery disease (21 vs 28%; $p=0.029$) or chronic renal disease (glomerular filtration rate ≤60 ml/min/1.73m2 in 16 vs 36%; $p<0.001$), and similarly likely to have diabetes (20 vs 17%; $p=0.36$) or COPD (23 vs 20%; $p=0.29$).

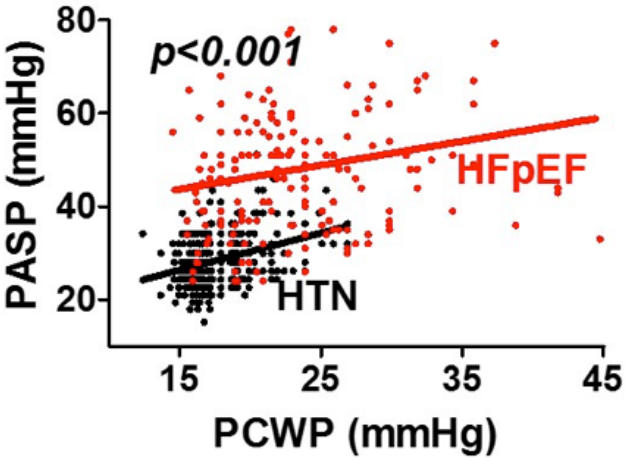


Figure 2: Association of pulmonary artery systolic pressure with pulmonary venous hypertension Pulmonary artery systolic pressure (PASP) increased with pulmonary capillary wedge pressure (PCWP) in patients with heart failure and preserved ejection fraction (HFpEF), as well as in subjects with hypertension (HTN) without heart failure, but remained higher in HFpEF than HTN after adjusting for PCWP ($p<0.001$). Raw data points and linear regression line for the association are shown for HFpEF (in red) and HTN (in black).

Distribution of PASP and Prevalence of PH

Median (25th, 75th percentile) PASP was 28 (24, 32) mmHg in HTN and 48 (37, 56) mmHg in HFpEF ($p<0.001$; Figure 1A). PH was present in 8% (N=38) of HTN and 83% (N=169) of HFpEF ($p<0.001$; Figure 1B). Clinical and echocardiographic characteristics of subjects with and without PH in each group are provided in Table 1. In both groups, patients with PH were older and had higher systolic blood pressure, wider pulse pressure, higher PCWP and larger left atria compared to those without PH. There was no difference in left ventricular systolic function (EF, stroke volume index, cardiac index) or structural characteristics (mass, relative wall thickness, volume) between those with and without PH in either group. Among HFpEF patients, the prevalences of atrial fibrillation, coronary artery disease, diabetes, chronic kidney disease and COPD were similarly high in those with and without PH.

Association of PASP with PCWP

PASP increased with PCWP in both HTN and HFpEF ($r = 0.318$ and 0.209 respectively; both $p<0.007$) (Figure 2). After adjusting for

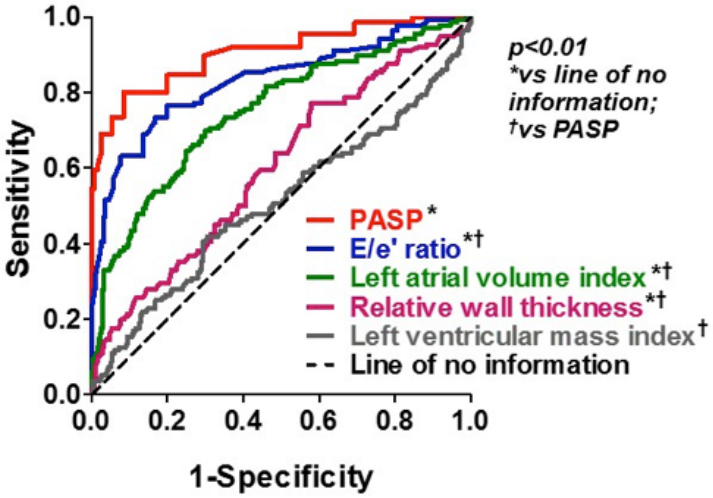
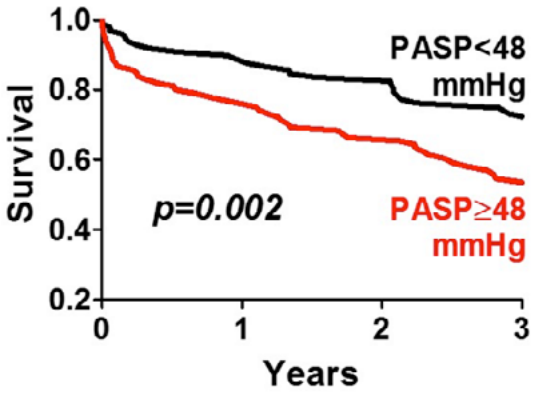


Figure 3: Receiver operating curves of echocardiographic parameters for the diagnosis of heart failure with preserved ejection fraction. By receiver operating curve analysis, echocardiographic parameters that distinguished heart failure with preserved ejection fraction (HFpEF) from hypertensive (HTN) heart disease without heart failure included pulmonary artery systolic pressure (PASP), E/e' ratio, left atrial volume index and relative wall thickness. The largest area under curve was obtained with PASP, with the optimal cutoff value of 35 mmHg.

PCWP, PASP was still higher in HFpEF compared to HTN ($p<0.001$), suggesting that beyond the post-capillary contribution of pulmonary venous congestion, a pre-capillary component of pulmonary arterial hypertension contributed to greater PH in HFpEF.

Utility of PASP in Distinguishing HFpEF from HTN

PASP distinguished HFpEF from HTN with an AUC of 0.91 ($p<0.001$) and optimal cutoff of 35 mmHg, coinciding with the definition of PH(17). The presence of PH (PASP > 35 mmHg) distinguished HFpEF from HTN with a sensitivity of 83% and specificity of 92%. In univariate analysis, other significant distinguishing markers included E/e', left atrial size and relative wall thickness, while left ventricular mass was not (Table 2). The largest AUC was obtained with PASP (Bonferroni adjusted $p<0.01$ vs each of the other markers in pairwise comparisons; Figure 3). In multivariate analysis involving the 443 subjects in whom all parameters were measurable, only PASP and E/e' remained significant



Number remaining				
PASP<48 mmHg	98	86	80	44
PASP≥48 mmHg	105	78	67	38

Figure 4: Kaplan-Meier survival curves in HFpEF patients with pulmonary artery systolic pressure above and below the median HFpEF patients with pulmonary artery systolic pressure (PASP) above the median value of 48 mmHg (in red) had reduced survival compared to patients with PASP<48 mmHg (in black) over 3 years (Log rank p=0.002).

markers of HFpEF (odds of HFpEF vs HTN = 1.22 times higher per 1 mmHg increase in PASP and 1.15 times higher per unit increase in E/e' respectively; both p<0.001). Excluding patients with atrial fibrillation (N=26 in HTN; N=54 in HFpEF) from the analysis gave similar results (data not shown).

Effect of PH on Survival

In HFpEF, there were 84 deaths over a median follow up of 2.8 years (mean 2.4±1.2 years). By Kaplan-Meier analysis, mortality was higher in those with a PASP above the median value of 48 mmHg (Log rank p=0.002; Figure 4). The presence of PH as defined by PASP above 35 mmHg was similarly strongly associated with mortality in HFpEF (Log rank p=0.003). Among echocardiographic parameters, only PASP was associated with mortality in HFpEF (unadjusted hazard ratio = 1.28 per 10 mmHg; p<0.001, Table 3) and this association persisted after adjustment for age (age-adjusted hazard ratio = 1.22 per 10 mmHg; p=0.005).

Table 2: Receiver Operating Curve Characteristics of Echocardiographic Parameters Distinguishing HFpEF from HTN

Parameter	Number Available	AUC (mean±SE)	P value	Optimal Cutoff	Sensitivity	Specificity
PASP, mmHg	673	0.91±0.02	<0.001	35	83	92
E/e' ratio	808	0.83±0.02	<0.001	12.5	70	85
Left atrial volume/ BSA, ml/m^2	848	0.75±0.02	<0.001	29	66	74
Relative wall thickness	759	0.60±0.03	<0.001	0.39	80	36
LV mass index, g/m^2	756	0.52±0.03	0.497	105	42	68

AUC, area under curve; PASP, pulmonary artery systolic pressure; BSA, body surface area;LV, left ventricular

Subanalysis Excluding Patients with COPD and Other Potential Causes of PH

Among subjects with measurable PASP, COPD was present in 15% (N=69) of HTN (13 with the clinical diagnosis of COPD, 67 with abnormal spirometry, 69 with either and 11 with both diagnostic criteria) and 32% (N=64) of HFpEF (46 with the clinical diagnosis of COPD, 34 with abnormal spirometry, 64 with either and 16 with both diagnostic criteria). Restricting the analysis to patients without COPD (N= 401 in HTN; N=139 in HFpEF), the HFpEF group still had greater prevalence of PH (83 vs 8%; p<0.001) and higher PASP (48±14 vs 28±5 mmHg; p<0.001) compared to HTN, even after adjusting for age and PCWP (p<0.001). PH remained a significant predictor of mortality in HFpEF (p=0.018) independent of age (age-adjusted hazard ratio =1.27 per 10 mmHg increase in PASP; p=0.014).

A further 11 HFpEF patients had other potential causes of PH (5 with obstructive sleep apnea, 4 with history of pulmonary embolism, 1 with scleroderma and 1 with liver disease). Excluding these subjects gave similar results, with greater prevalence of PH (82 vs 8%; p<0.001) and higher PASP (47±14 vs 28±5 mmHg; p<0.001) in HFpEF compared to HTN, even after adjusting for age and PCWP (p<0.001), as well as a negative impact of increasing PASP on survival in HFpEF, independent of age (age-adjusted hazard ratio =1.28 per 10 mmHg increase in PASP; p=0.019).

Table 3: Predictors of Mortality in HFpEF

Variable	Univariate Analysis*			Multivariate Analysis*		
	N	Hazard Ratio	P value	N	Hazard Ratio	P value
PASP, mmHg	203	1.28 per 10 mmHg	<0.001	136	1.20 per 10 mmHg	0.028
E/e' ratio	208	1.01 per unit	0.496	136	0.98 per unit	0.199
Left atrial volume/ body surface area, ml/m^2	185	1.12 per 10 ml/m^2	0.140	136	1.12 per 10 ml/m^2	0.237
Relative wall thickness	211	1.18 per 0.1 unit	0.108	136	1.26 per 0.1 unit	0.121
LV mass index, g/m^2	207	1.00 per 10 g/m^2	0.946	136	0.96 per 10 g/m^2	0.383

*Cox regression analysis, where multivariate model includes all five variables
PASP, pulmonary artery systolic pressure; LV, left ventricular

DISCUSSION

In these first population-based data regarding pulmonary pressures in HFpEF, PH was highly prevalent and often severe in HFpEF presenting in the general community. The development of PH was related to the extent of pulmonary venous hypertension as estimated by Doppler indices. However after accounting for this post-capillary component of PH, the severity of PH in HFpEF still exceeded that of hypertensive controls without HF from the same community, suggesting the contribution of a pre-capillary component of pulmonary arterial hypertension to PH in HFpEF. The severity of PH distinguished HFpEF from hypertensive controls with excellent diagnostic accuracy, superior to traditional indices of cardiac remodeling (left atrial volume, relative wall thickness, left ventricular mass) and of incremental value to Doppler indices of diastolic dysfunction (E/e'). Further, the presence of PH was a potent adverse prognostic factor in HFpEF, independent of age. The implications of these data for PH as a pathophysiologic factor and therapeutic target in HFpEF deserve further study.

Prevalence and Significance of PH in HFpEF

That severe PH could develop in HFpEF was described in early isolated case reports of elderly hypertensive patients with HFpEF(3,4). In a subsequent series of patients hospitalized in the New York metropolitan area for HFpEF, Klapholz et al(5) reported a mean PASP of 47±17 mmHg by echo in the 44% (272 of 619) of patients in whom measurements were available. More recently, Kjaergaard et al(7)

obtained echo PASP measurements in 38% (388 of 1022) of Danish patients hospitalized for symptomatic HF, 25% (N=96) of whom had preserved EF, and found a median (25th, 75th percentile) PASP of 39 (31, 50) mmHg. Of note, the latter study also identified elevated PASP as an independent predictor of mortality in HFpEF. While important, the generalizeability of these previous findings was limited by selection bias and the low proportions of patients in whom PASP estimates were available. Our current findings therefore serve to confirm and extend the prior studies by including all in- and out-patients with HFpEF presenting in the community, thus providing the first population-based estimates of the prevalence, severity and prognostic significance of PH in HFpEF to date.

Mechanism of PH in HFpEF

The development of PH in HFpEF has largely focused on the role of left ventricular diastolic dysfunction and the passive effect of pulmonary venous hypertension. Aragam et al(9) showed that in patients with aortic stenosis, most of whom had normal EF, it was the severity of diastolic dysfunction, rather than the severity of aortic stenosis, that correlated better with the severity of PH. Kessler et al(3) attributed the reversible severe PH in an elderly hypertensive man to abnormal left ventricular filling that was treated with long-acting nifedipine. Kjaergaard et al(7) alluded to the contribution of diastolic dysfunction to PH by showing that HF patients (25% HFpEF) with restrictive filling had higher PASP compared to those with non-restrictive patterns. Finally Bouchard et al(26) showed a close correlation between PASP and PCWP by echo in 69 patients with normal systolic function (not all with HF) and concluded that PASP could be used as a surrogate of left ventricular filling pressure when pulmonary vascular resistance was assumed normal. Our data, while consistent with the prior, importantly highlight that the passive contribution of pulmonary venous hypertension may not by itself account for the increased PASP in HFpEF compared to elderly hypertensives without overt HF. Beyond this post-capillary component of PH, we postulate that the greater severity of PH in HFpEF may be due to an additional pre-capillary component of pulmonary arterial hypertension. In longstanding pulmonary congestion, pre-capillary PH

may be mediated by reactive increases in pulmonary arterial tone or development of a congestive arteriopathy characterized by pulmonary arteriolar remodeling, medial hyperplasia and intimal fibrosis, as shown to occur in patients with mitral stenosis(10) or systolic HF(11). The presence of PH may therefore carry important clinical implications for the diagnosis and treatment of the syndrome as elaborated on below.

Diagnostic Utility

The difficulties and controversies surrounding the optimal diagnostic approach to HFpEF have been the subject of recent debate(27,28). In the most current consensus statement from the European Society of Cardiology(29), a variety of echocardiographic markers of diastolic dysfunction (chiefly the mitral E/e' ratio) or cardiac remodeling (left atrial size, left ventricular mass) were proposed to aid in the diagnosis of HFpEF. However, the specificity of these markers has been questioned, since elderly hypertensive patients frequently display abnormal mitral Doppler profiles and cardiac remodeling in the absence of clinical HF(15). As shown in our study and others(26), PASP elevation was a good surrogate measure of clinically significant pulmonary venous hypertension in HFpEF. The present data further demonstrated the utility of PH in distinguishing HFpEF from HTN independent of E/e', as well as its potent independent impact on survival, suggesting that PH may play a primary role in the pathophysiology of HFpEF. Importantly, these findings need to be prospectively validated in other populations, ideally using invasive gold-standard measurements.

Therapeutic Implications

The presence of a pre-capillary component in addition to post-capillary PH in HFpEF raises the potential that besides therapies aimed at reducing pulmonary venous congestion, those aimed at pulmonary arterial hypertension may also have a role in the treatment of HFpEF. To date, there are no proven therapies in HFpEF. Treatment recommendations as outlined in HF guidelines are empiric and have not changed over time. Specific therapy aimed at PH in HFpEF is therefore an appealing consideration but has been tempered by concern that increases in right heart output with pulmonary vasodilators may result

in further increases in left atrial pressure in patients with left heart disease and HF(30). Indeed, the use of epoprostenol was associated with increased mortality in systolic HF (31), although the mechanism for increased mortality was unclear. Similarly despite early data demonstrating the deleterious effect of endothelin and potential benefit of endothelin antagonism in HF, a trial of the selective endothelin receptor A antagonist darusentan in systolic HF failed to show clinical benefit (Anand I et al Lancet 2004;364:347). Yet there remains room for cautious optimism. Recent seminal trials employing phosphodiesterase 5 inhibitors in systolic HF (32,33), have demonstrated beneficial effects, including improvement in exercise capacity and quality of life. In fact, evidence exists that phosphodiesterase 5 inhibition may not only improve pulmonary tone and right heart function but may also exert pleiotropic effects on LV structure(34), ventricular function(34,35) and peripheral vascular function(36). These data lend support for the ongoing trial of phosphodiesterase-5 inhibition in HFpEF (Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure or RELAX trial; http://clinicaltrials.gov).

Limitations

The feasibility of obtaining tricuspid regurgitation signals may potentially have led to overestimation of the prevalence of PH, but estimations of PASP were obtained in the majority of subjects including a larger proportion of participants than in previous studies. While known causes of PH were excluded by careful clinical review in the subanalyses, occult diagnoses may have been missed in some patients. Lack of invasive measurements of pulmonary artery characteristic impedance or pulmonary arteriolar resistance precluded assessment of pulmonary artery stiffening or pulmonary arteriolar tone. However this study could not have been performed using an invasive approach. The potential limited precision of echo-derived PASP is acknowledged (18). Similarly, while the E/e' ratio provides an estimate of PCWP(19), it is not a perfect measure of PCWP. Further, resting measures of PCWP do not reflect activity related increases in PCWP which may contribute to reactive PH and congestive pulmonary arterial remodeling and weaken the correlation between resting PCWP and PASP. Finally, the single time-

point measurements in this study did not allow assessment for time-dependence of PASP in Cox regression analysis and may have led to underestimation of the prognostic significance of PH.

Conclusions

PH is common and can be severe in HFpEF presenting in the community. In addition to pulmonary venous hypertension from diastolic dysfunction, a component of pulmonary arterial hypertension may contribute to PH in HFpEF, distinguishing these patients from hypertensive controls without HF. The potent association between PH and mortality suggests that PH may contribute to the progression of HF in patients with HFpEF and thus PH may represent a therapeutic target in HFpEF.

ACKNOWLEDGEMENTS

Special thanks to Brian D. Lahr (Department of Biostatistics, Mayo Clinic, Rochester, MN) for his assistance with statistical analysis.

REFERENCES

1. Thompson W, White PD. Commonest Cause of Hypertrophy of the Right Ventricle-Left Ventricular Strain and Failure. Am Heart J 1936;12:641-649.
2. Abramson SV, Burke JF, Kelly JJ, Jr., et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116:888-95.
3. Kessler KM, Willens HJ, Mallon SM. Diastolic left ventricular dysfunction leading to severe reversible pulmonary hypertension. Am Heart J 1993;126:234-5.
4. Willens HJ, Kessler KM. Severe pulmonary hypertension associated with diastolic left ventricular dysfunction. Chest 1993;103:1877-83.
5. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 2004;43:1432-8.
6. Ghali JK, Kadakia S, Cooper RS, Liao YL. Bedside diagnosis of preserved versus impaired left ventricular systolic function in heart failure. Am J Cardiol 1991;67:1002-6.
7. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007;99:1146-50.
8. Shapiro B, Nishimura R, McGoon M, Redfield M. Diagnostic dilemmas: Diastolic heart failure causing pulmonary hypertension, pulmonary hypertension causing diastolic dysfunction. Adv Pulmon Hypertension 2006;5:13-20.
9. Aragam JR, Folland ED, Lapsley D, Sharma S, Khuri SF, Sharma GV. Cause and impact of pulmonary hypertension in isolated aortic stenosis on operative mortality for aortic valve replacement in men. Am J Cardiol 1992;69:1365-7.
10. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation 2000;102:1718-23.
11. Delgado JF, Conde E, Sanchez V, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 2005;7:1011-6.
12. Maurer MS, El Khoury Rumbarger L, King DL. Ventricular volume and length in hypertensive diastolic heart failure. J Am Soc Echocardiogr 2005;18:1051-7.
13. Melenovsky V, Borlaug B, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus non-failing hypertensive left ventricular hypertrophy in the urban Baltimore community. J Am Coll Card 2007;49:198-207.

14. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982-90.
15. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194-202.
16. Ommen SR, Nishimura RA, Hurrell DG, Klarich KW. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: a simultaneous catheterization and echocardiographic study. Mayo Clin Proc 2000;75:24-9.
17. Rich Se. Executive summary from the World Symposium on Primary Pulmonary Hypertension, Evian, France, September 6-10, 1998, co-sponsored by the World Health Organization.
18. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:14S-34S.
19. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-94.
20. Willens HJ, Chirinos JA, Gomez-Marin O, et al. Noninvasive differentiation of pulmonary arterial and venous hypertension using conventional and Doppler tissue imaging echocardiography. J Am Soc Echocardiogr 2008;21:715-9.
21. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79-108.
22. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107-36.
23. Miller A, Thornton JC, Warshaw R, Bernstein J, Selikoff IJ, Teirstein AS. Mean and instantaneous expiratory flows, FVC and FEV1: prediction equations from a probability sample of Michigan, a large industrial state. Bull Eur Physiopathol Respir 1986;22:589-97.
24. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256-76.
25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-45.
26. Bouchard JL, Aurigemma GP, Hill JC, Ennis CA, Tighe DA. Usefulness

of the pulmonary arterial systolic pressure to predict pulmonary arterial wedge pressure in patients with normal left ventricular systolic function. Am J Cardiol 2008;101:1673-6.

27. Maurer MS, Spevack D, Burkhoff D, Kronzon I. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? J Am Coll Cardiol 2004;44:1543-9.
28. Oh JK, Hatle L, Tajik AJ, Little WC. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. J Am Coll Cardiol 2006;47:500-6.
29. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.
30. Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. Journal of the American College of Cardiology 1994;24:982-988.
31. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44-54.
32. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol 2007;50:2136-44.
33. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555-62.
34. Takimoto E, Champion HC, Li M, et al. Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy. Nat Med 2005.
35. Borlaug BA, Melenovsky V, Marhin T, Fitzgerald P, Kass DA. Sildenafil inhibits beta-adrenergic-stimulated cardiac contractility in humans. Circulation 2005;112:2642-9.
36. Katz SD, Balidemaj K, Homma S, Wu H, Wang J, Maybaum S. Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol 2000;36:845-51.

Chapter 3

Pathophysiology of heart failure with preserved ejection fraction

3.3. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction.

Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. J Am Coll Cardiol. 2009 Jul 28;54(5):410-8

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ABSTRACT

Objectives: 1) Compare left ventricular (LV) systolic stiffness and contractility in normal subjects, hypertensives without heart failure, and patients with heart failure and preserved ejection fraction (HFpEF); and 2) Determine whether LV systolic stiffness or myocardial contractility are associated with mortality in HFpEF.

Background: Arterial load is increased in hypertension and is matched by increased end-systolic LV stiffness (ventricular-arterial coupling). Increased end-systolic LV stiffness may be mediated by enhanced myocardial contractility or processes which increase passive myocardial stiffness.

Methods: Healthy controls (n=617), hypertensives without HF (n=719) and patients with HFpEF (n=244, 96% hypertensive) underwent echo-Doppler characterization of arterial (Ea) and LV end-systolic (Ees) stiffness (elastance), ventricular-arterial coupling (Ea/Ees ratio), chamber-level and myocardial contractility (stress-corrected midwall shortening).

Results: Ea and Ees were similarly elevated in hypertensives with or without HFpEF compared with controls, but ventricular-arterial coupling was similar across groups. In hypertensives, elevated Ees was associated with enhanced chamber-level and myocardial contractility, while in HFpEF, chamber and myocardial contractility were depressed compared with both hypertensives and controls. Group differences persisted after adjusting for LV geometry. In HFpEF, impaired myocardial contractility (but not Ees) was associated with increased age-adjusted all-cause mortality.

Conclusions: While arterial load is elevated and matched by increased LV systolic stiffness in hypertension with or without HFpEF, the mechanisms of systolic LV stiffening differ substantially. These data suggest that myocardial contractility increases to match arterial load in asymptomatic hypertensive heart disease, but that progression to HFpEF may be mediated by processes which simultaneously impair myocardial contractility and increase passive myocardial stiffness.

INTRODUCTION

Half of patients with heart failure (HF) have a preserved ejection fraction (HFpEF)(1-4). HFpEF predominantly afflicts elderly, hypertensive patients(1,3,4). Vascular stiffness increases with age, promoting systolic hypertension and increased effective arterial elastance (Ea) (5,6). Left ventricular (LV) end-systolic stiffness (elastance, Ees) increases in tandem(5-7), such that the relationship between ventricular and arterial elastance (ventricular-arterial coupling) remains relatively constant(8-10).

End-systolic LV elastance is a measure of contractility, but it is also influenced by chamber geometry and passive myocardial stiffening(8,11). Ees is elevated in HFpEF(7,10), yet many(12-14), though not all(15) prior studies have reported that various systolic function indices are mildly depressed in HFpEF. Indeed, it is well recognized that impairments in myocardial contractility may coexist with preserved EF in hypertensives with concentric remodeling(16-20). This remodeling phenomenon allows preservation of endocardial motion despite reduced shortening of individual myofibers, such that the EF remains normal(19,21).

We sought to compare and contrast chamber and myocardial contractility, LV end-systolic stiffness and ventricular-arterial coupling in three groups of patients: 1) healthy controls without cardiovascular disease, 2) hypertensives without HF and 3) patients with HFpEF, using multiple load-independent measures of chamber and myocardial contractility. All participants were drawn from a large scale, non-selected, population-based sample. To account for differences in ventricular geometry, contractile indices were contrasted between each pattern of chronic chamber remodeling. To determine the clinical significance of these findings, relationships between contractility or LV systolic stiffness and mortality were examined.

METHODS

Study Population and Setting

The unique aspects of the Rochester Epidemiology Project for population-based research have been described(2,3). The study was approved by the Mayo Institutional Review Board.

A random sample (n=2042) of the Olmsted County, Minnesota population aged ≥45 years underwent echocardiography and record review. From this cohort, two control groups were identified(2,3,10): healthy, non-obese controls without cardiovascular disease or diabetes, and hypertensive controls without HF. From the same community, consecutive patients with HFpEF and no significant valvular disease were identified using the Framingham criteria(2,3). Vital status through March 2008 was determined from the Mayo Clinic registration database and the Rochester Epidemiology Project death database(2,3). Mortality data was ascertained from medical records, death certificates for Olmsted County residents, obituaries and notices of death in the local newspapers. Data on all Minnesota deaths were obtained from the State of Minnesota annually. Some clinical characteristics and ventricular function parameters from subjects in this study have previously been published(1-3,10), but most of the systolic indices and their associations with outcomes have not.

Echocardiography

Comprehensive echocardiographic assessment was performed by registered diagnostic cardiac sonographers using standardized instruments and techniques, with studies interpreted in a blinded fashion(10). Ventricular dimensions, wall thickness, chamber volumes, and stroke volume were determined in triplicate from 2-dimensional, M-mode echocardiography, and Doppler spectra using standard methods(10). Sex-specific definitions for ventricular hypertrophy and geometry patterns based on LV mass index and relative wall thickness (normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) were used(10). Left ventricular end-diastolic pressure was estimated from echo-Doppler and tissue-Doppler(10). Brachial blood pressure (BP) was determined by sphygmomanometry. End-systolic pressure was determined from the product of 0.9*systolic BP(8). Effective arterial elastance (Ea=end-systolic pressure/stroke volume) and circumferential end-systolic wall stress (cESS) were determined as measures of ventricular afterload(8,19).

Assessment of LV Systolic Chamber and Arterial Properties

Endocardial fractional shortening (eFS) was determined from two-dimensional systolic and diastolic dimensions. LV end-systolic elastance (Ees) was determined by the single beat technique(22). Ventricular-arterial interaction was quantified by the coupling ratio (Ea/Ees). To account for both afterload and preload, two additional load-independent measures of chamber contractility were examined: (1) wall-stress-corrected eFS (sc-eFS), determined by expressing observed eFS as a percentage of that predicted for any given wall stress, based upon the regression equation derived in the healthy controls(18); (2) preload recruitable stroke work (PRSW), determined using a validated single-beat technique(23).

Assessment of Myocardial Contractility

Measures of chamber-level contractility do not necessarily reflect myocardial contractility(16-19,21), because motion at the endocardial surface is greater than predicted by sarcomere shortening alone, due the phenomenon of cross-fiber shortening. Shortening of muscle fibers oriented in orthogonal directions at the inner and outer surfaces of the heart causes marked thickening in the radial axis(21). This effect is enhanced in the setting of concentric remodeling, allowing individual reductions in myofiber contraction to achieve the same net displacement of endocardium, preserving endocardial-based parameters such as EF(16,18,19,21). To assess myocardial contractility, circumferential midwall fractional shortening (mFS) was assessed using the two-shell method of Shimizu(16-19). To minimize afterload dependence, stress-corrected mFS (sc-mFS) was determined as a percentage of that predicted for any given wall stress using the regression equation derived from the healthy control population(18).

Statistical methods

Categorical variables were compared by the Chi-square test, and continuous variables were compared using one-way ANOVA with Bonferroni correction. Regression analysis was used to adjust for age, sex, body size, chamber size and morphology, or the presence of other diseases, where the dependent variable was the normally distributed

continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest. Any interaction between these variables was also evaluated and accounted for as appropriate. The Kaplan–Meier method tested for differences in survival between groups by the log-rank test. Cox proportional-hazards regression was used to adjust for confounding effects of age, body mass index, coronary disease, hypertension and diabetes mellitus on survival.

RESULTS

Subject Characteristics

Of 2042 randomly selected community residents, 617 met the criteria for the healthy control group and 719 subjects met the criteria for the hypertension without HF group. A total of 244 patients constituted the HFpEF group. Nearly all HFpEF patients had a history of hypertension,

Table 1: Subject characteristics

	Control (n=617)	**Hypertension** (n=719)	**HFpEF** (n=244)
Demographics			
Age (years)	57 (45-96)	66 (46-91)*	76 (22-99) *†
Female (%)	55	56	55
Body mass index (kg/m^2)	25.4±2.7	29.8±5.9*	32.2±20.7*†
Hypertension (%)	0	100*	96*
Coronary artery disease (%)	0	16*	53*†
Diabetes mellitus (%)	0	11*	37*†
Estimated Glomerular Filtration Rate ($ml/min/1.73m^2$)	74.4±14.1	74.7±37.0	64.3±28.1*†
Chronic Beta-Blocker use (%)	2	29*	74*†
Hemodynamics and LV Morphology			
Systolic BP (mmHg)	118±12	143±21*	132±23*†
Diastolic BP (mmHg)	70±8	76±11*	67±14†
LV mass index (g/m^2)	88.8±16.3	100.2±22.7*	102.1±29.0*
Relative wall thickness	0.38±0.06	0.42±0.07*	0.45±0.10*†
Percent with LV hypertrophy (%)	18	40*	42*

* $p<0.05$ vs CON; † $p<0.05$ vs HTN

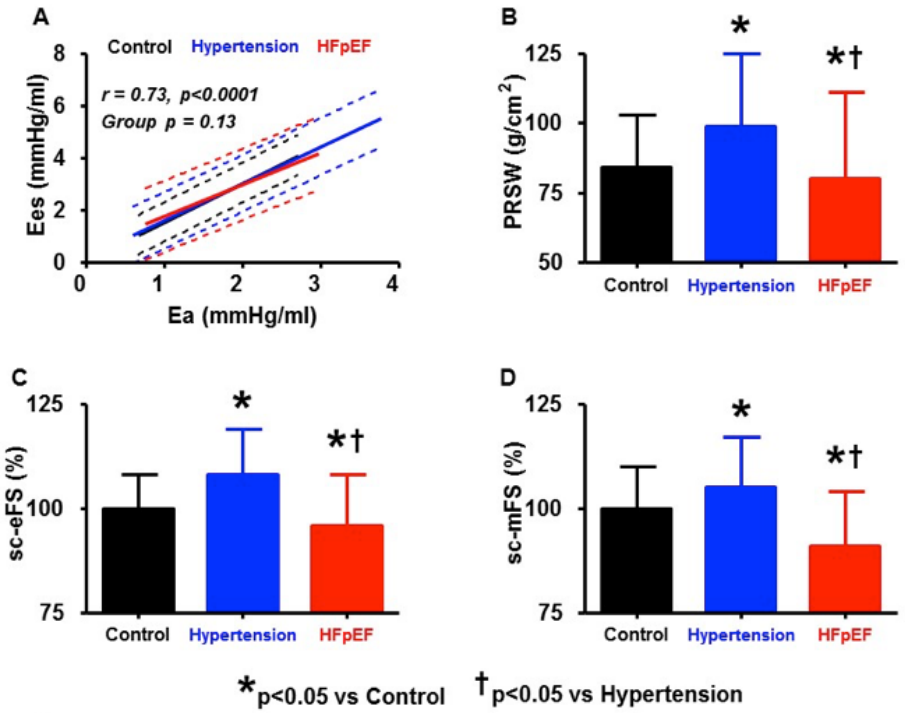

Figure 1. VA coupling and contractility: [A] The relationship between Ees and Ea was similar among each group (dashed lines show 95% prediction bands). [B-D] Load-independent chamber contractility (PRSW and sc-eFS) and myocardial contractility (sc-mFS) were elevated in hypertensives without HF and decreased in HFpEF compared with hypertensives and controls. Data are mean ± standard deviation.

and were older, more obese, and had higher prevalence of coronary artery disease and diabetes than hypertensives or controls (Table 1).

Ventricular-Arterial Stiffness and Coupling

Hypertensives and HFpEF displayed increased afterload (Ea and cESS) compared to controls (Table 2). While Ea was similarly increased in hypertensives and HFpEF, cESS was higher in HFpEF. As previously reported in this population(10), Ees was similarly increased in hypertensives and HFpEF compared with controls (Table 2). Overall, Ees was strongly correlated with Ea (Figure 1A), and both this relationship and the mean coupling ratios (Ea/Ees) were similar in all three groups (Table 2), indicating preserved ventricular-arterial coupling.

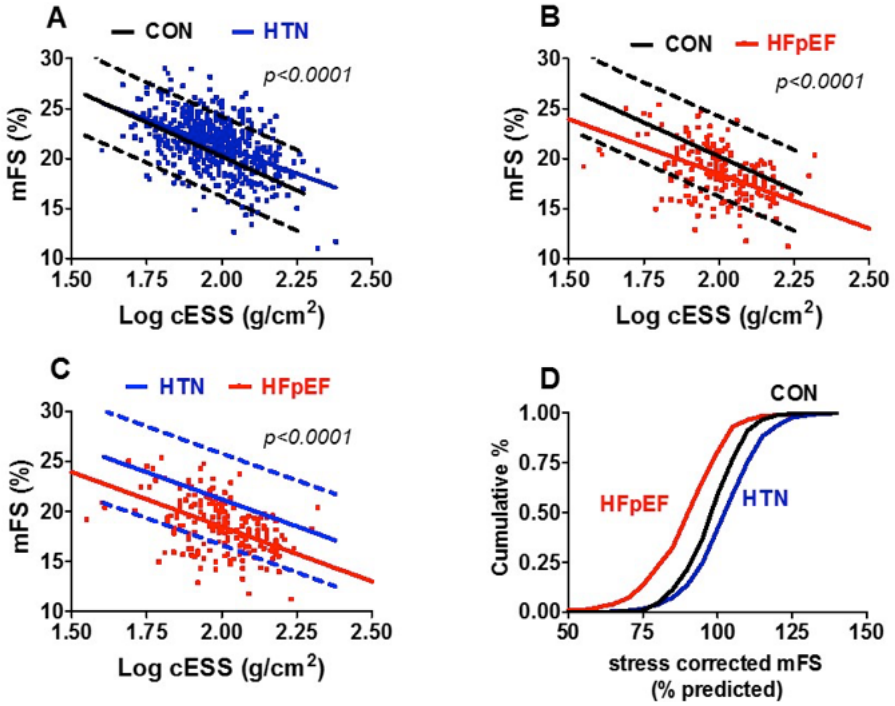

Figure 2. Myocardial contractility: [A] The relationship between midwall myofiber shortening (mFS) and end-systolic wall stress (log cESS) showing mean regression (solid) line and 95% confidence limits (dotted) in controls (black) with data points and regression line for hypertensives (blue) shifted upward, indicating enhanced myocardial contractility in hypertension. [B-C] In HFpEF (red), the data points and regression line are shifted down as compared to both controls and hypertensives, indicating depressed contractility**.** [D] Cumulative distribution plot for sc-mFS show that compared to healthy controls (black), myocardial contractility is depressed in HFpEF (red) and enhanced in hypertensives without HF (blue).

LV Chamber and Myocardial Systolic Properties

As compared to controls, EF was similar but eFS and mFS were higher in the hypertensive group. In contrast, in HFpEF, EF, eFS and mFS were reduced as compared to hypertensives or controls (Table 2). Similarly, load-independent measures of chamber contractility (PRSW and sc-eFS) were higher in hypertensives as compared to controls and lower in HFpEF compared with hypertensives or controls (Table 2, Figure 1). Adjusting for wall stress (cESS), mFS was higher in hypertensives compared to controls (Figure 2A) and lower in HFpEF compared to controls (Figure 2B) and hypertensives (Figure 2C). HFpEF displayed

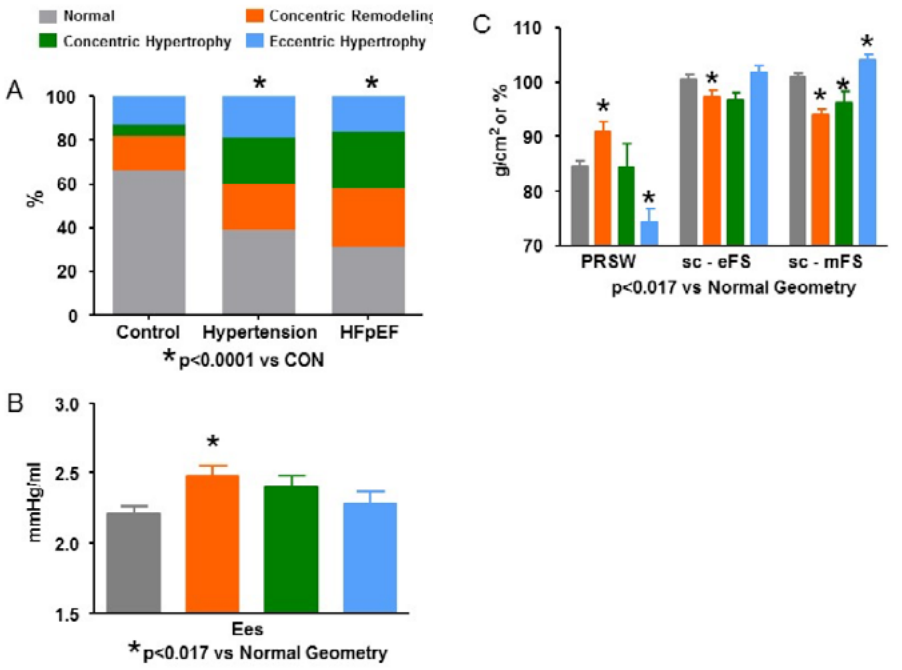

Figure 3: Geometry and its effect on end-systolic elastance and contractility indices: [A] The distributions of LV geometry differed among controls, hypertensives and HFpEF. Even within the healthy control group, Ees varied according to geometry pattern [B], as did PRSW, sc-eFS and sc-mFS [C]. See text for discussion. Data are mean ± standard error.

lower sc-mFS than hypertensives or controls (Table 2, Figure 1), even after adjusting for age, gender, body size, renal function, beta-blocker use, history of coronary disease and diabetes ($p<0.0001$). The cumulative distribution of sc-mFS was shifted rightward from controls in hypertension and leftward in HFpEF (Figure 2D), indicating that myocardial contractility was systematically enhanced in hypertensives and impaired in HFpEF.

Relationships of Geometry to Contractility

As previously described in this cohort(3,10), relative wall thickness increased from controls to hypertension to HFpEF (Table 1). The prevalence of left ventricular hypertrophy was similarly increased in hypertensives and HFpEF. The distribution of geometry among hypertensives and HFpEF patients was different from that of control

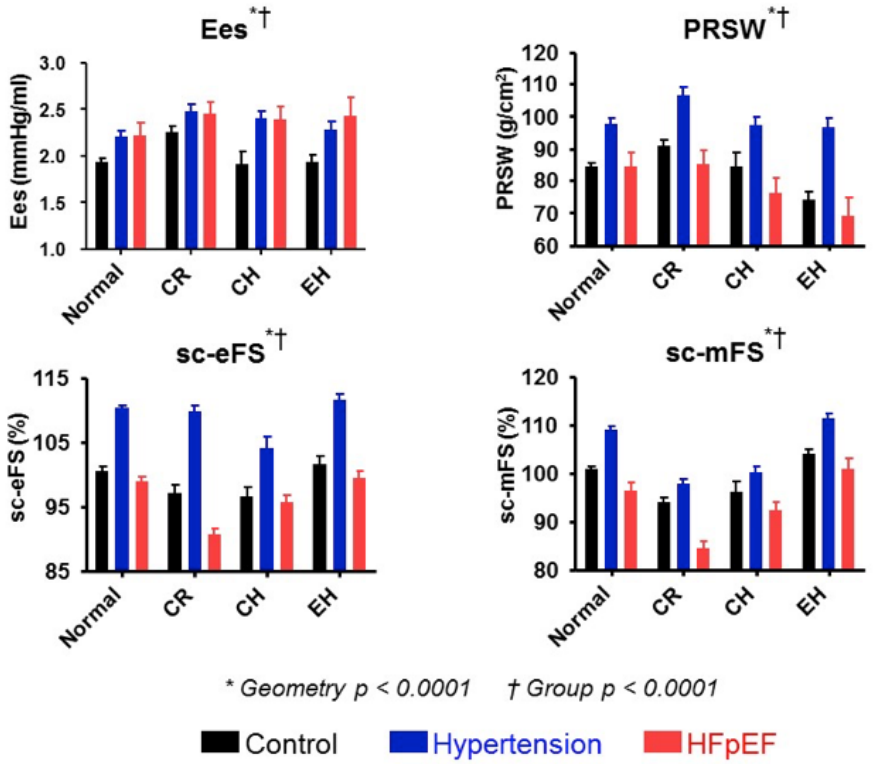

Figure 4: VA coupling and contractility according to group and geometry: [A] Ees was elevated in HFpEF (red) and hypertensives (blue) compared with controls (black) for each pattern of geometry. In contrast, PRSW [B], sc-eFS [C] and sc-mFS [D] were each consistently depressed in HFpEF and elevated in hypertensives compared with controls. CR, concentric remodeling; CH, concentric hypertrophy; EH, eccentric hypertrophy. See text for discussion. Data are mean ± standard error.

patients (Figure 3A), and tended to be different in HFpEF versus hypertensives (p=0.045).

In healthy controls, Ees (Figure 3 B) and most contractile indices (Figure 3 C) were systematically elevated or reduced as a function of chamber geometry alone. To adjust for confounding effects of chamber remodeling between the groups, we compared Ees and each contractile index within each geometry pattern. Figure 4 shows that, regardless of geometry, Ees was consistently elevated in hypertensives and HFpEF as compared to controls, while PRSW, sc-eFS and sc-mFS were each consistently higher in hypertensives as compared to controls and lower in HFpEF as compared to both hypertensives and controls.

Table 2: Load, Contractility and Ventricular-Arterial Coupling

	Control (n=617)	Hypertension (n=719)	HFpEF (n=244)
LV Afterload			
cESS (kdyne/cm^2)	90.8±21	98.9±28.5*	105.5±35.4*†
Ea (mmHg/ml)	1.30±0.30	1.50±0.41*	1.53±0.43*
Ventricular arterial coupling			
Ees (mmHg/ml)	1.99±0.59	2.30±0.80*	2.42±0.90*
Ea/Ees	0.68±0.13	0.68±0.17	0.69±0.22
Systolic Function			
EF (%)	63±5	65±6	62±6*†
eFS (%)	39.7±5.1	41.3±5.7*	35.9±6.6*†
mFS (%)	20.9±2.5	21.5±2.7‡	18.5±3.0*†
Load-Independent Measures Contractility			
PRSW (g/cm^2)	84.5±18.6	99.3±25.5*	78.7±31.1*†
sc-eFS (% predicted)	100±8	108±11*	96±12*†
sc-mFS (% predicted)	100±10	105±12*	91±13*†

*p<0.005 vs CON; †p<0.0001 vs HTN (unadjusted)

cESS=circumferential end-systolic stress, Ea=effective arterial elastance, Ees=end-systolic elastance, EF=ejection fraction, eFS=endocardial fractional shortening, mFS=midwall fractional shortening, PRSW=preload-recruitable stroke work, sc=stress-corrected.

Myocardial Contractility and Outcomes

Median follow-up was 3.1 years (mean 3.1 ± 0.6 years) in the HFpEF group. Mortality at 3 years was 36.4% in HFpEF, 3.1% in hypertension, and 0.8% in controls. In the HFpEF group, survival decreased with greater impairment of myocardial contractility (Figure 5). After adjusting for age, sc-mFS below the median was associated with a 33% increase in mortality (p =0.013). Impaired sc-mFS remained a significant predictor of mortality after adjusting for age, body mass index, coronary disease, hypertension and diabetes mellitus (p=0.01). In contrast, EF, Ees, Ea, and geometry pattern were not associated with age-adjusted mortality (p>0.05).

DISCUSSION

This is the largest population-based study to date examining left ventricular systolic properties in HFpEF, exploring the mechanisms

underlying ventricular-arterial coupling in hypertensive heart disease according to the presence or absence of HFpEF. Among hypertensives, increases in end-systolic LV stiffness were associated with increased chamber and myocardial contractility. In contrast, similar increases in HFpEF patients were associated with impaired contractility, suggesting that elevated Ees may be related to passive myocardial stiffening to a greater extent in this group. Disparities in contractile function were not due to differences in chamber geometry, and impaired myocardial contractility in HFpEF was associated with increased mortality. We speculate that over time, patients with hypertensive heart disease who develop HFpEF acquire structural or functional perturbations which impair myocardial contractility, and that these perturbations contribute to the transition to and progression of overt HF, despite preserved EF.

Ventricular-Arterial coupling

The interaction of the heart with the arterial system (ventricular-arterial coupling) is a key determinant of cardiovascular performance(8,9). Ea is a lumped parameter reflecting total arterial afterload, incorporating mean and pulsatile components. Ees is determined invasively from the slope and intercept of the end-systolic pressure-volume relationship, but may also be measured noninvasively(22), allowing Ees to be determined in larger patient populations. Ventricular-arterial coupling is expressed by the Ea/Ees ratio(8).

While EF is the most commonly utilized measure of systolic function in clinical practice, it is potently influenced by loading conditions and chamber remodeling(24,25). EF is more accurately conceptualized as a measure of ventricular-arterial coupling. Under normal circumstances, the Ea/Ees ratio varies from 0.5-1.0, a range where cardiac work and efficiency are optimized(8,9). While normal ventricular-arterial coupling ratios (and EF) were observed in each patient group, there were dramatic differences in the ways in which coupling was maintained—enhanced contractility in hypertensives without HF but impaired contractility in HFpEF.

It is well recognized that changes in contractile performance alter Ees(22,24) but Ees is also influenced by chamber geometry, and by factors which alter the passive stiffness of the myocardium(8,11).

With aging, increases in arterial stiffness are associated with tandem increases in both systolic and diastolic LV stiffness(5,6,8). Indeed, in this study population, we have previously reported that diastolic ventricular stiffness is elevated in both hypertensives and HFpEF compared with healthy controls, but is highest in HFpEF(10). Taken together with the current findings of impaired contractility despite elevated Ees in HFpEF, we speculate that the processes which contribute to diastolic stiffening in HFpEF influence systolic stiffness as well.

Contractility and Coupling in HFpEF

Seminal reports from the 1980's and 90's demonstrated that abnormal myocardial contractility may coexist with a normal EF, because concentric geometric chamber remodeling preserves the extent of endocardial motion relative to the diastolic cavity size(16-19,21). A number of studies have reported abnormalities in regional systolic function in HFpEF, particularly shortening in the longitudinal axis(12,26-29). However, the significance of these findings has been questioned(30), because systolic velocities vary inversely with afterload(31), typically elevated in HFpEF patients(8,10), and because longitudinal shortening does not fully reflect chamber-level contractility(30). Examining load-independent parameters of chamber and myocardial contractility in a large, population-based study, we show that patients with HFpEF indeed do display systolic dysfunction compared with both hypertensives without HF and healthy controls.

Two important but smaller-sized studies also found that roughly a third of HFpEF patients fell below the 95% prediction bands for the relationship between mFS and cESS observed in healthy controls(14,15). More importantly, over 90% of HFpEF patients fell below the mean regression line describing healthy controls. This is consistent with the systematic shift in the distribution of myocardial contractility in HFpEF observed in the current study. However, prior studies did not compare HFpEF with hypertensive controls, HFpEF subjects were highly selected, there were no adjustments for differences in LV geometry, and the impact of impaired myocardial contractility on survival was not examined.

Ees increases with decreasing LV size, yet even after adjusting

for differences in geometry, Ees remained significantly elevated in HFpEF, while each additional load-independent index of chamber-level and myocardial contractility was impaired. This "disconnect" between Ees and other measures of contractility has been observed in animal models of pressure overload HF, where increased Ees coexists with impaired chamber, myocardial and myocyte contractility, fibrosis, diastolic dysfunction and impaired beta adrenergic signaling(32). The association of resting contractile dysfunction with increased mortality in HFpEF, viewed in light of these animal studies and recent studies demonstrating abnormal contractile reserve with stress in HFpEF(33-35) indicates that impaired contractility, however mild at rest, may not simply be an innocuous bystander in HFpEF, but rather may reflect processes which mediate progression to overt HF.

Contractility and Coupling in Hypertension without HF

Hypertension is a dominant risk factor for HFpEF(1,4), and many of the cardiovascular features in HFpEF are also seen in asymptomatic hypertensives(13,33). As such, comparisons between these two groups provide valuable mechanistic insight into what specifically distinguishes the HFpEF phenotype. While elevated Ees in HFpEF coexisted with impaired contractility, elevated Ees was associated with enhanced contractility in hypertensives. Earlier studies have reported reduced myocardial contractility in hypertension, and that the presence of impaired myocardial contractility is associated with higher rates of cardiovascular events(36). However, the patient groups populating these earlier referral-based studies were often pre-selected for the presence of hypertrophy, and had more extreme levels of concentric remodeling(13,16,18,19). We also found that sc-mFS was categorically impaired in the presence of concentric relative to normal geometry—regardless of patient group (Figures 3 and 4). However, within each geometry pattern, contractility was consistently enhanced in hypertensives without HF. The hypertensive patients in the current study were younger than HFpEF, and it may be that most of the hypertensive controls in this population-based study were at an "earlier" stage of disease, where enhanced contractility may be observed as has been reported in human (37,38) and animal studies(39). Alternatively, hypertensives in this more contemporary, population-based study may

have been more optimally treated(40), since the extent of concentric remodeling was not as extreme as seen in earlier referral-based studies. If hypertensive heart disease and HFpEF exist in a continuum as has been suggested(10), it may be that the processes leading to concomitant loss of contractile hyper-function and passive stiffening play a role in the transition from hypertension to clinically-evident HFpEF. Alternatively, the myocardial response to pressure overload may differ in patients predisposed to develop HFpEF. These concepts merit future investigation in longitudinal studies.

Study Limitations

The methods employed to assess systolic function are validated against gold standard techniques(10,22,23), but echo-Doppler data inherently have greater variability compared with invasive measurements. While sampling bias was minimal in this population-based study, our study cohort was almost exclusively white, and these results may not be applicable to other ethnic groups. Cause of death data is not available from this population, and we are unable to determine how impaired contractility might be related to mode of death. These data are observational in nature and therefore cannot prove causality or temporal progression.

Conclusions

While ejection fraction and ventricular-arterial coupling are similarly "normal" in hypertensives with or without HFpEF, the mechanisms whereby LV systolic elastance increases to match arterial load differs according to the presence of HF. Patients with hypertension without HF display enhanced Ees and contractility, while Ees in HFpEF is elevated despite impaired contractility, at both the chamber and myocardial levels. These differences are independent of geometry, and myocardial contractile dysfunction is associated with increased mortality in HFpEF, emphasizing its clinical importance. Therapies targeting processes which mediate concomitant contractile dysfunction and passive stiffening may prove useful in the treatment of patients with HFpEF.

REFERENCES:

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
2. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. Jama 2003;289:194-202.
3. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. Jama 2006;296:2209-16.
4. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 2004;43:1432-8.
5. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. J Am Coll Cardiol 1998;32:1221-7.
6. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation 2005;112:2254-62.
7. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714-20.
8. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Heart Fail Clin 2008;4:23-36.
9. Chantler PD, Lakatta EG, Najjar SS. Arterial-Ventricular Coupling: Mechanistic Insights into Cardiovascular Performance at Rest and During Exercise. J Appl Physiol 2008.
10. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982-90.
11. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501-12.
12. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with “isolated” diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195-201.
13. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial

remodeling/dysfunction. J Am Coll Cardiol 2007;49:198-207.

14. Vinch CS, Aurigemma GP, Simon HU, Hill JC, Tighe DA, Meyer TE. Analysis of left ventricular systolic function using midwall mechanics in patients >60 years of age with hypertensive heart disease and heart failure. Am J Cardiol 2005;96:1299-303.
15. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation 2005;111:2306-12.
16. Shimizu G, Hirota Y, Kita Y, Kawamura K, Saito T, Gaasch WH. Left ventricular midwall mechanics in systemic arterial hypertension. Myocardial function is depressed in pressure-overload hypertrophy. Circulation 1991;83:1676-84.
17. Shimizu G, Zile MR, Blaustein AS, Gaasch WH. Left ventricular chamber filling and midwall fiber lengthening in patients with left ventricular hypertrophy: overestimation of fiber velocities by conventional midwall measurements. Circulation 1985;71:266-72.
18. de Simone G, Devereux RB, Roman MJ, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol 1994;23:1444-51.
19. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195-202.
20. Rosen BD, Edvardsen T, Lai S, et al. Left ventricular concentric remodeling is associated with decreased global and regional systolic function: the Multi-Ethnic Study of Atherosclerosis. Circulation 2005;112:984-91.
21. de Simone G, Devereux RB. Rationale of echocardiographic assessment of left ventricular wall stress and midwall mechanics in hypertensive heart disease. Eur J Echocardiogr 2002;3:192-8.
22. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028-34.
23. Lee WS, Huang WP, Yu WC, Chiou KR, Ding PY, Chen CH. Estimation of preload recruitable stroke work relationship by a single-beat technique in humans. Am J Physiol Heart Circ Physiol 2003;284:H744-50.
24. Kass DA, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships. Circulation 1987;76:1422-36.
25. Konstam MA. “Systolic and diastolic dysfunction” in heart failure? Time for a new paradigm. J Card Fail 2003;9:1-3.
26. Petrie MC, Caruana L, Berry C, McMurray JJ. “Diastolic heart failure” or

heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002;87:29-31.

27. Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002;87:121-5.
28. Brucks S, Little WC, Chao T, et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol 2005;95:603-6.
29. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008.
30. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation 2006;113:296-304.
31. Borlaug BA, Melenovsky V, Redfield MM, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol 2007;50:1570-7.
32. Perrino C, Naga Prasad SV, Mao L, et al. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. J Clin Invest 2006;116:1547-60.
33. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138-47.
34. Ennezat PV, Lefetz Y, Marechaux S, et al. Left ventricular abnormal response during dynamic exercise in patients with heart failure and preserved left ventricular ejection fraction at rest. J Card Fail 2008;14:475-80.
35. Borlaug BA, Lam CSP, Olson TP, Flood KS, Johnson BD, Redfield MM. Cardiovascular Reserve Function in Heart Failure with Preserved Ejection Fraction: Systolic versus Diastolic Determinants. Circulation (abs) 2008.
36. de Simone G, Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH. Midwall left ventricular mechanics. An independent predictor of cardiovascular risk in arterial hypertension. Circulation 1996;93:259-65.
37. Hartford M, Wikstrand JC, Wallentin I, Ljungman SM, Berglund GL. Left ventricular wall stress and systolic function in untreated primary hypertension. Hypertension 1985;7:97-104.
38. Palatini P, Bongiovi S, Mario L, Schiraldi C, Mos L, Pessina AC. Above-normal left ventricular systolic performance during exercise in young subjects with mild hypertension. Eur Heart J 1995;16:232-42.
39. Jegger D, da Silva R, Jeanrenaud X, et al. Ventricular-arterial coupling in a rat model of reduced arterial compliance provoked by hypervitaminosis

D and nicotine. Am J Physiol Heart Circ Physiol 2006;291:H1942-51.

40. Perlini S, Muiesan ML, Cuspidi C, et al. Midwall mechanics are improved after regression of hypertensive left ventricular hypertrophy and normalization of chamber geometry. Circulation 2001;103:678-83.

Chapter 3

Pathophysiology of heart failure with preserved ejection fraction

3.4. Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction.

Lam CS, Brutsaert DL. J Am Coll Cardiol. 2012 Oct 30;60(18):1787-9

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Heart failure with preserved ejection fraction (HFPEF) is becoming the dominant form of heart failure in developed countries.(1) Yet, there remain fundamental gaps in our understanding of the pathophysiology of HFPEF(2) and we still do not have evidence-based therapies to reduce morbidity and mortality in HFPEF.

The study by Akiyama et al highlights a potential novel target in HFPEF. In this observational hospital-based study of 321 patients with HFPEF and 173 age-, sex- and comorbidity- matched controls, endothelial function was assessed using reactive hyperemia peripheral arterial tonometry. Endothelial dysfunction (defined by a reactive hyperemia index below the median value of 0.49) was independently associated with HFPEF, as were higher body mass index and lower glomerular filtration rate. In HFPEF, endothelial dysfunction predicted cardiovascular events over a mean follow-up of 20 months, independently of clinical (age, diabetes, hospitalization, NYHA status), echocardiographic (E/e', EF) and neurohormonal (BNP) factors. Of note, the study population consisted of patients referred to two tertiary centers in Japan, was more predominantly male (50%), and had better outcomes than observed in Western cohorts.(1) Whether this was due to selection bias or true ethnic differences could not be ascertained. Nonetheless, the strong prognostic significance of endothelial dysfunction in HFPEF suggested that the association was not merely a passive observation, but that endothelial dysfunction may have actively contributed to the pathophysiology and progression of HFPEF.

Endothelial dysfunction

The endothelium plays an obligatory role in cardiovascular homeostasis by regulating cardiac function and vasomotor tone, adjusting vascular permeability, and preserving blood fluidity.(3) Endothelial dysfunction is clinically assessed as a deficient vasodilatory response to various stimuli, indicating impaired endothelium-mediated NO bioavailability. In the study by Akiyama et al, the stimulus used was the surge of blood flow following release of brachial artery cuff occlusion (endothelium-dependent flow mediated dilatation), and the hyperemic response was measured in the peripheral vasculature. This methodology is simple and non-invasive, offering the potential

for widespread clinical application, but provides only a narrow view of overall endothelial function. A comprehensive assessment of endothelial function requires consideration of the endothelium as an integrated system involving not only the peripheral vasculature of the systemic circulation, but also the central circulation, including the cardiac (myocardial capillary and endocardial) and pulmonary vascular endothelium (Figure 1A).(3) The findings of Akiyama et al may be viewed as a mere reflection of a more general dysfunction of the entire endothelial system in heart failure, for only if placed in such a broader context will these peripheral vascular measurements genuinely contribute to our insights into the pathophysiology of HFPEF.

Cardiovascular risk factors and endothelial dysfunction

When viewed as a single system integrated within other organ systems of the body, the endothelium forms the first point of contact between circulating blood-borne factors and adjacent organ tissues. In the presence of cardiovascular risk factors such as diabetes, dyslipidemia, and hypertension, redox imbalances induce oxidative stress that causes endothelial dysfunction,(4) even in the absence of end-organ damage. Akiyama et al matched their patients and controls for diabetes and hypertension, but still found more endothelial dysfunction in patients with HFPEF who were notably more obese than controls. Obesity is associated with marked endothelial dysfunction which has recently been shown to be related to increased activity of the pro-inflammatory cytokine TNF-α (promoting superoxide generation and reducing NO bioavailability in visceral adipose vasculature).(5) HFPEF is increasingly recognized as an inflammatory condition, mediated in large part by obesity.(6) The higher levels of high-sensitivity C-reactive protein in the HFPEF group of the study by Akiyama et al support this concept.

Peripheral vascular endothelium

While there are ample experimental and clinical data showing that both peripheral and central endothelial dysfunction contribute to the pathogenesis of heart failure,(7) most of this evidence pertains to heart failure with reduced ejection fraction. In skeletal muscle, endothelial

dysfunction in both conductive and resistance vessels may explain exercise intolerance – the cardinal manifestation of heart failure irrespective of ejection fraction. In HFPEF, Borlaug et al(8) found a high prevalence of endothelial dysfunction and blunted exercised-induced augmentation in peripheral blood flow in association with reduced exercise capacity. Similarly, Akiyama et al observed poorer NYHA status in those with impaired endothelial function, underscoring the functional significance of endothelial dysfunction in HFPEF. Furthermore, endothelial dysfunction may impact the renal vasculature.(9) The extent to which renal vascular endothelial dysfunction contributed to the lower glomerular filtration rates in patients with HFPEF compared to matched controls in the study by Akiyama et al deserves further study.

Central cardiac endothelium

Beyond endothelial cells in various peripheral organs, endothelial cells in the heart warrant consideration for their role in HFPEF.(3) These include endothelial cells of the coronary vessels, but more importantly of the intramyocardial capillaries and endocardium where endothelial cells directly communicate with subjacent cardiomyocytes. The contribution of the cardiac endothelium, in conjunction with the pulmonary vascular endothelium (Figure 1A), is of critical importance since this represents the largest endothelial surface of the body, and serves as the greatest single source of endothelial mediators.(3) Indeed, in experimental post-infarction settings, both cardiac(10) and pulmonary vascular(11) endothelial dysfunction have been shown to contribute to the development of heart failure. In the setting of HFPEF however, data are scarcer. The key risk factors for HFPEF, namely hypertension and diabetes, are associated with evidence of endocardial and myocardial capillary endothelial abnormalities in experimental models,(12, 13) and these abnormalities may explain the impaired left ventricular relaxation in pressure-overload hypertrophy.(14) The coronary endothelium has been shown to modulate left ventricular diastolic function via paracrine effects in healthy humans and post-transplant patients.(15) More work is needed to better understand how cardiac endothelial dysfunction contributes to the pathophysiology of human HFPEF.

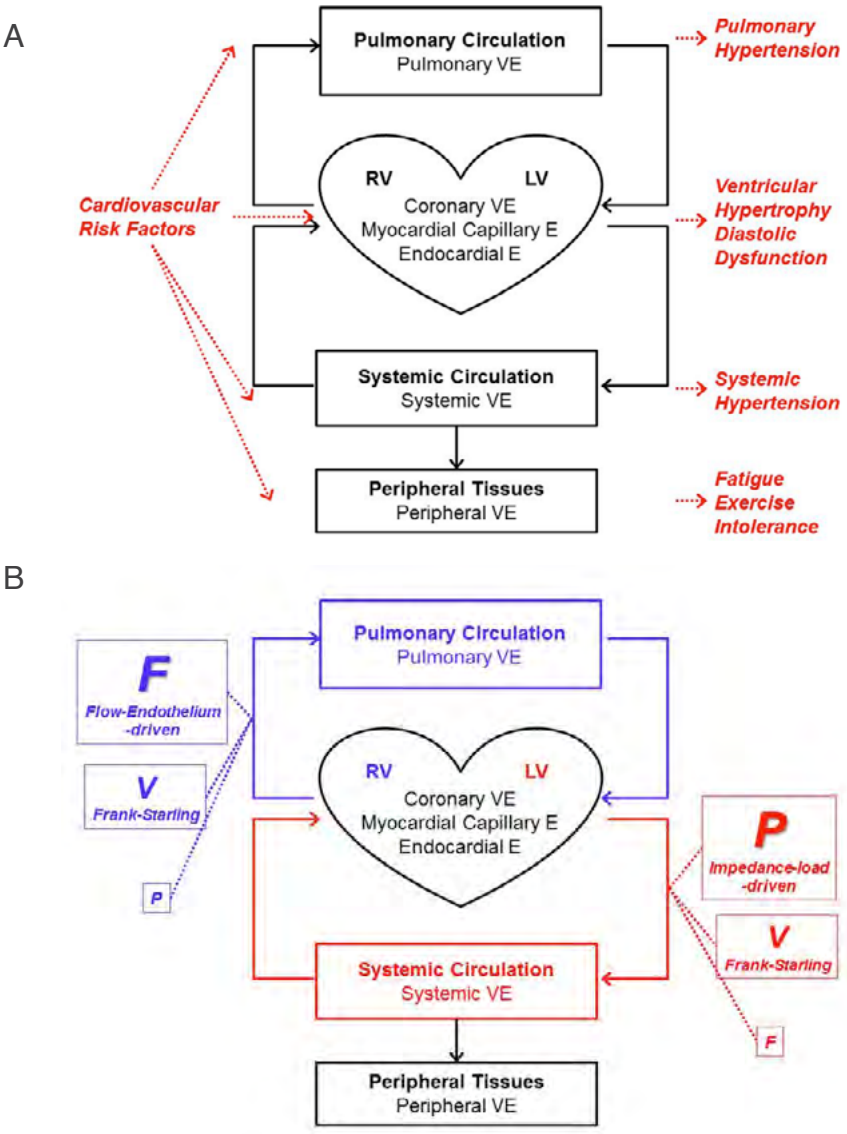

Figure 1. The endothelial system in heart failure with preserved ejection fraction (HFPEF) The cardiovascular endothelial system integrates the peripheral vascular endothelium (VE) with the central cardiac endothelium (consisting of coronary VE, myocardial capillary endothelium and endocardial endothelium) and pulmonary VE. *Modified from (3)* [**A**] The endothelium is at the interface between circulating cardiovascular factors and underlying organ tissues. Oxidative stress causes endothelial activation, endothelial dysfunction and organ-level dysfunction which may be observed in patients with HFPEF (red italics). [**B**] The relative contribution of endothelial dysfunction to the pulmonary versus systemic circulations may differ. Considering hemodynamic factors of pressure (P), volume (V) and flow (F), the predominantly flow-endothelium dependent pulmonary circulation (blue) may be more susceptible to shear stress and endothelial dysfunction compared to the predominantly pressure-load dependent systemic circulation (red).

Systemic versus pulmonary circulation

Combined ventricular and vascular stiffening, involving both the systemic and pulmonary circulations, is known to play a role in the pathophysiology of HFPEF.(16, 17) In the systemic circulation, endothelial dysfunction, detectable in healthy individuals with normal brachial blood pressure, is associated with increased central pulse pressure and systemic arterial stiffening,(18) This suggests that systemic endothelial dysfunction may be a primary phenomenon in the development of frank systemic hypertension and its pathophysiologic consequences of increased left ventricular wall stress, hypertrophy, diastolic dysfunction and HFPEF. In the pulmonary circulation, endothelial dysfunction has similarly been detected as an early event leading to the development of pulmonary hypertension in the setting of experimental heart failure.(11) The presence of pulmonary hypertension is an ominous development in the progression of HFPEF.(17) While endothelial dysfunction may be the common substrate underlying parallel changes in the systemic and pulmonary circulations, the relative contributions of endothelial dysfunction in the two circulations may differ: The pulmonary circulation, being primarily flow-driven in contrast to the pressure-driven systemic circulation, may be more susceptible to the influence of shear stress and endothelial dysfunction (Figure 1B).

Conclusions

A significant pathophysiologic role of endothelial dysfunction in HFPEF, as supported by data from Akiyama et al, suggests that endothelial dysfunction may be a potential therapeutic target. Indeed, many of the actions of endothelium-derived NO are attributable to activation of the cGMP pathway -- a pathway targeted by compounds such as sildenafil and LCZ696 which are currently being tested in therapeutic trials in HFPEF. Results of these trials are eagerly anticipated and may shed more light on the importance of endothelial function in HFPEF.

REFERENCES

1. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail. 2011 Jan;13(1):18-28.
2. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation. 2011 May 10;123(18):1996-2004; discussion 5.
3. Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. Physiol Rev. 2003 Jan;83(1):59-115.
4. Taddei S, Ghiadoni L, Virdis A, Versari D, Salvetti A. Mechanisms of endothelial dysfunction: clinical significance and preventive non-pharmacological therapeutic strategies. Curr Pharm Des. 2003;9(29):2385-402.
5. Virdis A, Santini F, Colucci R, Duranti E, Salvetti G, Rugani I, et al. Vascular generation of tumor necrosis factor-alpha reduces nitric oxide availability in small arteries from visceral fat of obese patients. J Am Coll Cardiol. 2011 Jul 12;58(3):238-47.
6. Franssen C, Paulus WJ. The future diagnosis of heart failure with normal ejection fraction: less imaging, more biomarkers? Eur J Heart Fail. 2011 Oct;13(10):1043-5.
7. Ferrari R, Bachetti T, Agnoletti L, Comini L, Curello S. Endothelial function and dysfunction in heart failure. Eur Heart J. 1998 Jul;19 Suppl G:G41-7.
8. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010 Sep 7;56(11):845-54.
9. Bassenge E. Endothelial function in different organs. Prog Cardiovasc Dis. 1996 Nov-Dec;39(3):209-28.
10. Qi XL, Stewart DJ, Gosselin H, Azad A, Picard P, Andries L, et al. Improvement of endocardial and vascular endothelial function on myocardial performance by captopril treatment in postinfarct rat hearts. Circulation. 1999 Sep 21;100(12):1338-45.
11. Ben Driss A, Devaux C, Henrion D, Duriez M, Thuillez C, Levy BI, et al. Hemodynamic stresses induce endothelial dysfunction and remodeling of pulmonary artery in experimental compensated heart failure. Circulation. 2000 Jun 13;101(23):2764-70.
12. Chu GX, Ling Q, Guo ZG. Effects of endocardial endothelium in myocardial mechanics of hypertrophied myocardium of rats. Zhongguo Yao Li Xue Bao. 1995 Jul;16(4):352-6.
13. Popov D, Sima A, Stern D, Simionescu M. The pathomorphological alterations of endocardial endothelium in experimental diabetes and diabetes associated with hyperlipidemia. Acta Diabetol. 1996 Mar;33(1):41-

7.

14. MacCarthy PA, Shah AM. Impaired endothelium-dependent regulation of ventricular relaxation in pressure-overload cardiac hypertrophy. Circulation. 2000 Apr 18;101(15):1854-60.
15. Paulus WJ. Paracrine coronary endothelial modulation of diastolic left ventricular function in man: implications for diastolic heart failure. J Card Fail. 1996 Dec;2(4 Suppl):S155-64.
16. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation. 2007 Apr 17;115(15):1982-90.
17. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009 Mar 31;53(13):1119-26.
18. McEniery CM, Wallace S, Mackenzie IS, McDonnell B, Yasmin, Newby DE, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. Hypertension. 2006 Oct;48(4):602-8.

Chapter 3

Pathophysiology of heart failure with preserved ejection fraction

3.5. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community.

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ABSTRACT

Background: Heart failure (HF) is a clinical syndrome characterized by signs and symptoms involving multiple organ systems. Longitudinal data demonstrating that asymptomatic cardiac dysfunction precedes overt HF are scarce, and the contribution of non-cardiac dysfunction to HF progression is unclear. We hypothesized that subclinical cardiac and non-cardiac organ dysfunction would accelerate the manifestation of HF.

Methods and Results: We studied 1038 participants of the Framingham Heart Study original cohort (mean age 76±5 years; 39% men) with routine assessment of left ventricular (LV) systolic and diastolic function. Major non-cardiac organ systems were assessed using serum creatinine (renal), serum albumin (hepatic), ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) (pulmonary), hemoglobin concentration (hematologic/oxygen carrying capacity) and white blood cell count (systemic inflammation). On follow-up (mean 11 years), there were 248 incident HF events (146 in women). Adjusting for established HF risk factors, antecedent LV systolic (hazards ratio 2.33; 95%CI, 1.43–3.78) and diastolic (hazards ratio 1.32; 95%CI, 1.01-1.71) dysfunction were associated with increased HF risk. Adjusting for cardiac dysfunction, higher serum creatinine, lower FEV1:FVC ratios and lower hemoglobin concentrations were associated with increased HF risk (all $P<0.05$); serum albumin and white blood cell count were not. Subclinical dysfunction in each non-cardiac organ system was associated with a 30% increased risk of HF ($P=0.013$).

Conclusions: Antecedent cardiac and non-cardiac organ dysfunction are associated with increased incidence of HF, supporting the notion that HF is a progressive syndrome and underscoring the importance of non-cardiac factors in its occurrence.

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by a constellation of signs and symptoms involving multiple organ systems such as the heart (classic 'pump failure'), the lungs (dyspnea), the kidneys (salt and water retention) and the liver (congestion). Current HF guidelines1, 2 emphasize the importance of asymptomatic cardiac dysfunction as a preceding stage in the progression to clinically overt HF. Cross-sectional studies have demonstrated the presence of asymptomatic systolic or diastolic LV dysfunction in the community in individuals at risk of, but without HF,3 and an even higher prevalence of these abnormalities in patients with overt HF.4 However, to demonstrate a prospective association between these structural precursors and future HF, longitudinal studies are needed.

Importantly, the current HF staging system1 does not specifically acknowledge the potential association of non-cardiac dysfunction with the occurrence of HF. Since the syndrome of HF involves multiple organ systems, even mild functional derangement of a non-cardiac organ system may accelerate the manifestation of overt HF, particularly when other organ systems are also involved. Indeed, emerging evidence suggests that subclinical renal impairment,5 hypoalbuminemia,6, 7 decline in pulmonary function,8, 9 anemia10 and systemic inflammation11 may all contribute to HF progression. Of note, the prevalence of non-cardiac co-morbidities is high among patients with overt HF, and these co-morbidities are major determinants of mortality after the onset of HF.12, 13

The relations of antecedent cardiac and non-cardiac dysfunction (i.e. present before onset of overt HF) to the incidence of HF have not been studied comprehensively in the community. In a previous report,14 we described the prevalence and prognosis of asymptomatic LV systolic dysfunction in the community but that investigation did not examine the association of LV diastolic dysfunction or of non-cardiac major organ system dysfunction with the risk of HF. Accordingly, we aimed to prospectively determine the association of cardiac and non-cardiac dysfunction with the incidence of HF among older adults without HF in the community. To achieve this, we harnessed the unique availability of longitudinal data and routine surveillance in the Framingham Heart

Study. We hypothesized that subclinical dysfunction in both cardiac and non-cardiac organ systems would accelerate the manifestation of HF. Further recognizing potential mechanistic differences between HF with reduced ejection fraction (HFREF) versus HF with preserved ejection fraction (HFPEF), we also hypothesized that the types of antecedent subclinical organ system dysfunction may differ according to the type of incident HF (HFREF versus HFPEF).

METHODS

Participants

The Framingham Heart Study is a longitudinal community-based cohort study that began in 1948.15 The original cohort has been under continuous surveillance and participants are examined at the Heart Study clinic approximately every 2 years. In the present investigation, we included participants attending the 20th biennial examination with routine assessment by Doppler echocardiography, but without prevalent HF (Supplementary Figure 1). Since our focus was on subclinical organ dysfunction, we excluded participants with overt organ dysfunction such as those with overt renal failure (defined as a serum creatinine>2 mg/dL [176.8 µmol/l]; N=12). All participants provided written informed consent and the study protocol was approved by the Institutional Review Board of the Boston University Medical Center.

Definition of cardiac dysfunction

Established HF risk factors modeled as covariates included age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease. LV systolic dysfunction was assessed by echocardiographic ejection fraction estimated visually.14 LV diastolic dysfunction was defined on the basis of LV filling pattern as any abnormal relaxation, pseudonormal filling or restrictive filling. Abnormal relaxation (mitral E/A<0.5, deceleration time>280 ms) or restrictive filling (mitral E/A>2.0, deceleration time<120 ms) was classified based on mitral inflow patterns.16 In the absence of tissue Doppler imaging, pseudonormal LV filling was distinguished from normal LV diastolic function by the presence of any of the following: left atrial size ≥ sex-

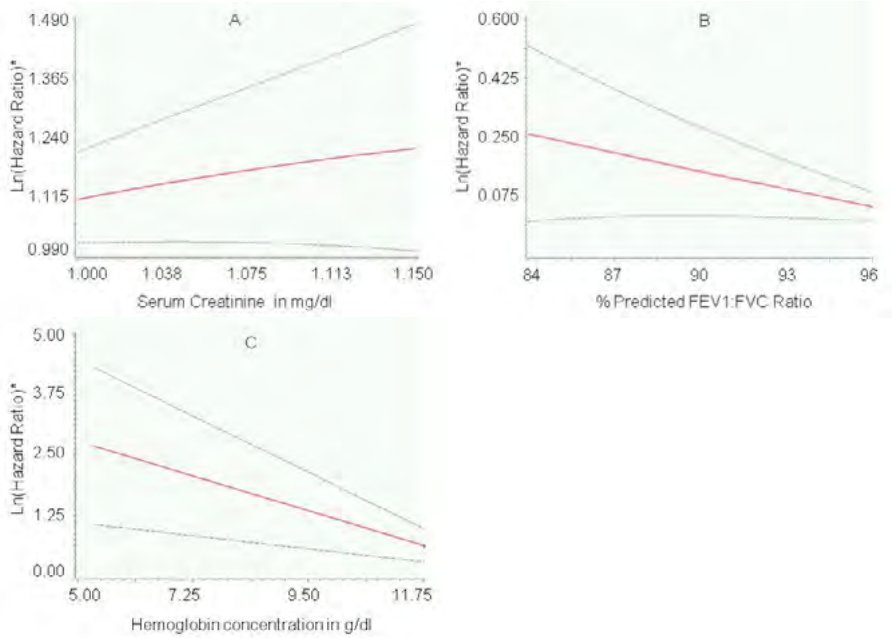

Figure 1. Association of measures of major non-cardiac organ system function with risk of incident heart failure Generalized additive models with penalized splines were used to assess the association of multivariable-adjusted hazards ratio for heart failure with (A) serum creatinine concentration, (B) ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1:FVC ratio) and (C) hemoglobin concentration. Lines indicate means (solid) and 95% confidence intervals (dotted). *Y-axes represent multivariable-adjusted Ln (hazards ratio). To obtain serum creatinine concentration in µmol/l, multiply values in mg/dl by 88.4.

specific 80th percentile, LV mass ≥ sex-specific 80th percentile, or any atrial fibrillation. These criteria closely parallel recommendations from the European Society of Cardiology (ESC) for the diagnosis of HFPEF,17 and use the upper sex-specific quintiles of left atrial size and LV mass to characterize atrial enlargement and LV hypertrophy,18 respectively, in our elderly cohort. Both LV systolic and diastolic dysfunction were modeled as binary variables (presence versus absence).

Definition of non-cardiac major organ system dysfunction

We evaluated non-cardiac major organ systems that could accelerate the manifestations of HF (dyspnea, fluid retention/pedal edema, and exertional fatigue). Participants underwent routine spirometry and phlebotomy. Measurement variables used to define non-cardiac

function included:5-7, 10, 11

- Renal system: serum creatinine.
- Hepatic system: serum albumin concentration.
- Pulmonary system: ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) expressed as % predicted for age and sex.
- Hematologic system/oxygen carrying capacity: hemoglobin concentration.
- Systemic inflammation: white blood cell count.

These non-cardiac function variables were modeled as both continuous and as binary variables (see below). The sample size for analyses of non-cardiac dysfunction variables was smaller (n=676) than the overall sample with available echocardiographic measures of LV systolic and diastolic function (n=1038; Supplementary Figure 1).

Outcome

Participants have been under ongoing, routine surveillance for incident HF since the baseline examination in 1987-1990. HF was defined as satisfying the previously published Framingham criteria19 (presence of 2 major, or of one major plus two minor criteria) and adjudicated by a panel of three experienced investigators. The ejection fraction closest to the date of the HF event was used to categorize HF into HFPEF (EF>45%) or HFREF (EF≤45%).20 Measurements of ejection fraction performed at HF onset, during HF hospitalization, or within 1 year of HF onset in the absence of intervening myocardial infarction were eligible.20

Statistical analyses

We used Cox proportional hazards regression models to assess the relationship of cardiac and non-cardiac dysfunction variables to the incidence of HF after confirming that the assumption of proportionality of hazards was met. Covariates eligible for the multivariable model included LV systolic and diastolic dysfunction, continuous measures of non-cardiac function (defined above), as well as established HF risk factors (defined above).

For each non-cardiac function variable (including those found to be not significant), we initially examined generalized additive models with penalized splines to assess potential non-linearity of the association.21 None of the associations were found to be non-linear. Therefore, we proceeded to model linear associations in Cox models. In the absence of any non-linearity of the associations, we also used a priori cut-points based on the lower 25th or upper 75th percentile of each continuous variable in order to create binary variables defining organ "dysfunction" for incorporation into a risk score. The risk score for non-cardiac dysfunction was then calculated for each participant by allocating 1 point for each affected non-cardiac organ system that was significantly associated with the risk of HF. This scoring system approach assumes that the hazards posed by dysfunction in each of the non-cardiac systems are similar (weighted the same), and offers a simple, practical score that may be meaningfully applied in clinical settings. The association of the non-cardiac risk score with incident HF was then plotted using Kaplan-Meier curves, and assessed using Cox proportional hazards modeling adjusting for established HF risk factors (noted above) and cardiac dysfunction variables.

Finally, analyses were repeated separately for incident HFREF as the outcome (and censoring cases of HFPEF at the time of that event), or incident HFPEF as the outcome (and censoring cases of HFREF at the time of that event). Cox proportional hazards regression was used, in which variables entered into the model included LV systolic and diastolic dysfunction, measures of non-cardiac function, as well as established HF risk factors noted above. Valvular heart disease was excluded in the analysis for HFPEF consistent with current diagnostic criteria,17 and included as a covariate in the analysis for HFREF.

All analyses were performed using SAS and a two-sided P value of <0.05 was used to indicate statistical significance. All authors had full access to the data and take responsibility for the integrity of the data.

RESULTS

Baseline characteristics

The study sample consisted of 1038 elderly participants (Table 1). More

than three-quarters of the sample was hypertensive and about half was on antihypertensive treatment. The prevalence of asymptomatic LV systolic and diastolic dysfunction were 5% and 36%, respectively, consistent with other community-based studies.3 The distributions of measures of non-cardiac function were within the ranges expected for elderly individuals in the general population.5

Cardiac dysfunction as a risk factor for incident HF

Over a mean follow-up of 11 years, there were 248 incident first HF events (146 in women; 119 HFREF, 101 HFPEF, EF was not available for 28 HF events). In multivariable models adjusting for established

Table 1. Baseline characteristics

Characteristics	
N	1038
Age, yrs	76±5
Men, no.,(%)	409 (39)
Cardiovascular risk factors	
Body mass index, kg/m^2	26.6±4.5
Systolic blood pressure, mmHg	147±22
Hypertension, no., (%)	799 (77)
Hypertension treatment, no., (%)	551 (53)
Total cholesterol:HDL ratio	4.85±1.65
Diabetes mellitus, no., (%)	104 (10)
Myocardial infarction, no, (%)	96 (9)
Valve disease, no., (%)	41 (4)
Cardiac function	
LV systolic dysfunction, no., (%)	57 (5)
LV diastolic dysfunction,*no., (%)	372 (36)
Non-cardiac function	
Serum creatinine , mg/dl	0.93±0.23
Serum albumin, g/dl	4.23±0.36
FEV1:FVC ratio, % predicted	96.9±10.9
Hemoglobin concentration, g/dl	14.0±1.5
White blood cell count, x10^9/l	6.8±2.3

Values are mean±SD unless otherwise stated. Serum creatinine concentration can be converted to µmol/l by multiplying the value in mg/dl by 88.4. HDL, high-density lipoprotein; LV, left ventricular; EF, ejection fraction; FEV1:FVC, ratio of forced expiratory volume in 1 second to forced vital capacity expressed as % predicted for age and sex * Diastolic dysfunction included any abnormal relaxation (mitral E/A<0.5, deceleration time>280 ms); pseudonormal LV filling (distinguished from normal LV diastolic function by the presence of any of the following: left atrial size ≥ sex-specific 80th percentile [4.8 cm in men, 4.4 cm in women], LV mass ≥ sex-specific 80th percentile [158.4 g/m2 in men, 141.9 g/m2 in women], or any atrial fibrillation); or restrictive filling (mitral E/A>2.0, deceleration time<120 ms).

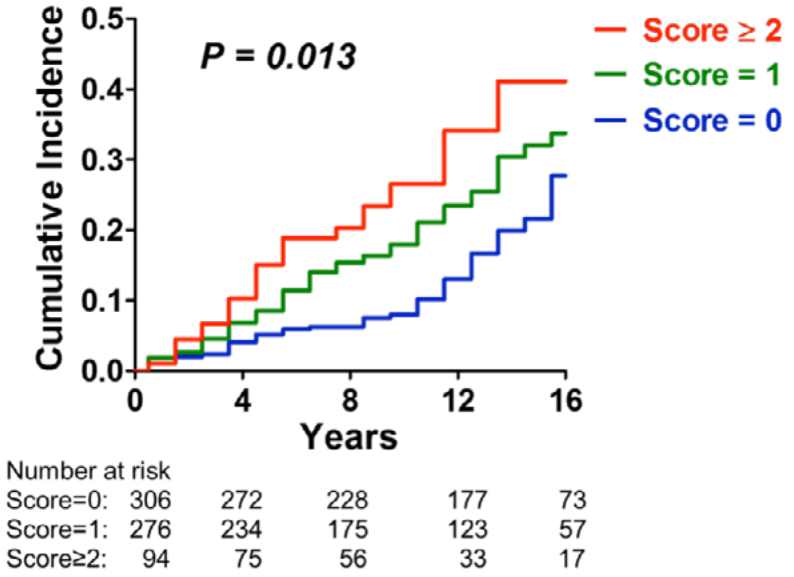

Figure 2. Cumulative incidence of incident heart failure according to non-cardiac major organ system dysfunction risk score The non-cardiac organ system dysfunction risk score awarded 1 point for the presence of each of the following (range 0-3): serum creatinine >1.05 mg/dl (92.8 µmol/l), ratio of forced expiratory volume in 1 second to forced expiratory volume <91% predicted, hemoglobin concentration <13 g/dl. Increasing non-cardiac risk score at baseline was associated with increasing risk of incident heart failure (HF) in our community-based sample (log rank *P* value = 0.013).

HF risk factors (age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease), both LV systolic dysfunction and LV diastolic dysfunction were associated with increased risk of incident HF (Table 2).

Non-cardiac risk factors and major organ system dysfunction risk score for incident HF

Participants (n=676; mean age 75±5 years; 42% men) without missing non-cardiac risk factor variables had similar baseline characteristics (body mass index, systolic blood pressure, diabetes) compared to those with missing variables (all P>0.05). Adjusting for established HF risk factors and presence of cardiac systolic and diastolic dysfunction, higher serum creatinine, lower FEV1:FVC ratios and lower hemoglobin concentrations were associated with increased risk of new-onset

Table 2. Cardiac Dysfunction as a risk factor for incident heart failure

Characteristic	Hazards ratio (95%CI)	*P* value*
LV systolic dysfunction	2.33 (1.43–3.78)	<0.001
LV diastolic dysfunction	1.32 (1.01-1.71)	0.039

LV, left ventricular
*Adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease in 1038 participants (248 HF events)

HF (Table 3). There was no association between serum albumin concentration (P=0.306) or white blood cell count (P=0.685) and incident HF. Individual Cox proportional hazards models with penalized splines for serum creatinine, FEV1:FVC ratio and hemoglobin did not reveal non-linearity for the association with HF risk (Figure 1). A risk score for non-cardiac dysfunction was calculated, therefore, using pre-determined cut-points (based on 25th or 75th percentiles of the variables in the sample, as defined above), and awarding 1 point for each affected organ system (range 0-3); regression coefficients for these variables were comparable in the multivariable models, further justifying their similar weighting in the score (Table 3). Of note, the cut-points used to define organ "dysfunction" were within the ranges frequently observed in ambulatory elderly individuals from the general population.5 Increasing non-cardiac risk score at baseline was positively associated with risk of HF (Figure 2).

In secondary analyses, results were similar when estimated glomerular filtration rate (eGFR by MDRD equation) was used instead of serum creatinine (hazards ratio for each 1SD decrease in eGFR was

Table 3. Non-cardiac risk factors and risk score for incident heart failure

Characteristic	Hazards ratio (95% CI)*	*P* value*	Cut-off percentile	Cut-off value	Points awarded
Serum creatinine	1.21 (1.01–1.45)	0.036	>75th percentile	> 1.05 mg/dl (>92.8 µmol/l)	1
FEV1:FVC ratio	1.21 (1.02–1.43)	0.029	<25th percentile	< 91 % predicted	1
Hemoglobin concentration	1.24 (1.09–1.40)	<0.001	<25th percentile	< 13 g/dl	1

FEV1:FVC, ratio of forced expiratory volume in 1 second to forced vital capacity
*Hazards ratio are for 1SD increase in serum creatinine, 1SD decrease in FEC1:FVC ratio and 1 unit decrease in hemoglobin concentration, adjusting for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, valvular heart disease, and left ventricular systolic and diastolic function in 676 participants without any missing variables (170 HF events)

1.24 (95% CI, 1.03-1.50; P=0.026) adjusting for established HF risk factors and presence of cardiac dysfunction). Other biomarkers of non-cardiac dysfunction (blood urea nitrogen, total bilirubin, transaminases, hematocrit, C-reactive protein measured by traditional assays [high sensitivity assays unavailable], uric acid) were also tested for their associations with incident HF in secondary analyses, and results are shown in Supplementary Table 1. These secondary analyses supported the original selection of creatinine, albumin, FEV1:FVC ratio and hemoglobin as simple, convenient and widely available biomarkers to include in the final risk score. We also performed sensitivity analyses using difference percentile cutpoints to define the risk score (tertiles instead of quartiles) and found similar results (data not shown).

Multivariable risk factors for all incident HF, HFREF and HFPEF

In multivariable modeling for all incident HF, LV systolic dysfunction, LV diastolic dysfunction and the non-cardiac risk score were each associated with incident HF, adjusting for established HF risk factors (Table 4). There was no significant interaction between non-cardiac

Table 4. Association of cardiac and non-cardiac dysfunction with incident heart failure

Characteristics	Hazards ratio (95%CI)*	*P* value*
All incident HF		
LV systolic dysfunction	1.97 (1.05–3.68)	0.034
LV diastolic dysfunction	1.40 (1.02-1.93)	0.039
Non-cardiac risk score† per 1 unit increase	1.30 (1.06-1.60)	0.013
Incident HFREF		
LV systolic dysfunction	3.93 (1.86 – 8.30)	<0.001
Serum creatinine per 1SD increase	1.32 (1.04 – 1.69)	0.025
Hemoglobin concentration per 1unit decrease	1.31 (1.10 – 1.55)	0.002
Incident HFPEF		
LV diastolic dysfunction	1.88 (1.13 – 3.13)	0.016
FEV1:FVC ratio per 1SD decrease	1.38 (1.04 – 1.83)	0.024

HF, heart failure; LV, left ventricular; HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction; FEV1:FVC, ratio of forced expiratory volume in 1 second to forced vital capacity

*Adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, cholesterol, diabetes mellitus, prior myocardial infarction, and valvular heart disease (valvular heart disease excluded for HFPEF) in 676 participants without any missing variables (170 total HF events: 82 HFREF, 66 HFPEF, 22 EF unavailable).

†Components of the non-cardiac risk score are described and their individual hazards ratios are shown in Table 3.

risk score and the presence of LV systolic or diastolic dysfunction (P=0.78 and 0.84 respectively). In multivariable modeling for HFREF and HFPEF separately, antecedent LV systolic dysfunction, greater serum creatinine and lower hemoglobin concentration were associated with incident HFREF; whereas antecedent LV diastolic dysfunction and lower FEV1:FVC ratio were associated with incident HFPEF, adjusting for established HF risk factors (Table 4).

In further analyses adjusting for smoking and excluding participants with overt pulmonary dysfunction (FEV1/FVC < 60%; N=3), hypoalbuminemia (albumin < 2.5 g/dL; N=0, no participant had hypoalbuminemia) or anemia (hemoglobin < 10.5g/dL; N=7), results were essentially unchanged (data not shown). Using an EF cutpoint of 50% (instead of 45%) to distinguish HFPEF from HFREF revealed similar results (Supplementary Table 2).

DISCUSSION

Principal findings

In our prospective study of a large, community-based sample, antecedent subclinical cardiac and non-cardiac major organ system dysfunction were associated with risk of future HF. The presence of asymptomatic LV systolic and diastolic dysfunction preceded and increased the risk of incident HF by more than two-fold and more than 30%, respectively. These findings support the emphasis in current HF guidelines regarding the progressive nature of HF and importance of recognizing preceding asymptomatic cardiac dysfunction. Our data also extend the previous HF staging system by providing evidence for the association of non-cardiac dysfunction with progression to clinical HF. Adjusting for cardiac dysfunction, the presence of subclinical renal impairment, airflow limitation or anemia was each associated with 30% increased risk of incident HF. Finally, antecedent LV systolic dysfunction was associated with future HFREF, whereas antecedent LV diastolic dysfunction was associated with future HFPEF. Further, subclinical renal impairment and lower hemoglobin concentrations were associated with a higher incidence of HFREF, whereas baseline airflow obstruction was related positively to the risk of future HFPEF. The implications of these findings for the early identification of individuals at

risk of HF, and potential strategies to prevent progression to overt HF, deserve further study.

Left ventricular systolic and diastolic dysfunction and risk of HF

Previous cross-sectional studies have provided evidence for the existence of asymptomatic LV dysfunction in the general community (Stage B HF in the American College of Cardiology/ American Heart Association classification system),3, 22 as well as increased prevalence and severity of LV dysfunction in patients with clinical HF (Stage C HF).3, 4 While these cross-sectional data supported the proposed stages of the HF, prior studies were limited by potential reverse causality, since assessment of LV function was performed at the same point in time as the diagnosis of clinical HF. Further, cross-sectional studies may be criticized for scientific circularity of reasoning in that the presence of LV systolic or diastolic dysfunction is used to make the diagnosis HFREF or HFPEF, respectively. Prospective data are needed to resolve these issues. In the Cardiovascular Health Study,23 LV systolic and diastolic dysfunction predicted incident HF over a mean follow-up of 5.2 years. However, the relations between the type of LV dysfunction (systolic versus diastolic) and the type of HF (HFREF versus HFPEF) were not assessed. More recently, researchers from the Mayo Clinic reported a 2-year HF incidence rate of 1.9% in a selected sample of 82 patients with preclinical diastolic dysfunction.24 Patients with systolic dysfunction were not studied. Our current data are consistent with these prior data and extend previous knowledge by demonstrating that LV systolic dysfunction predicts future HFREF, whereas LV diastolic dysfunction portends HFPEF. The current data, therefore, help to fill the knowledge gap linking Stage B to Stage C in the American College of Cardiology/ American Heart Association classification scheme, whether referring to HFREF or HFPEF.

Non-cardiac dysfunction and risk of HF

HF is a clinical syndrome characterized by a constellation of signs and symptoms involving multiple organ systems besides the heart. Thus, even mild functional derangement of a non-cardiac organ system, which in itself is not severe enough to produce symptoms,

may accelerate the manifestation of overt HF particularly when other organ systems are also involved. A decline in renal function affects sodium handling and fluid homeostasis, thus increasing the propensity to manifest fluid overload.5 Pulmonary function has a direct impact on the manifestation of dyspnea. Subclinical chronic pulmonary disease is characterized by low-grade inflammation and may contribute to progression of atherosclerosis and myocardial dysfunction,8 while even mild airflow obstruction is associated with abnormal LV diastolic filling.9 Anemia affects the oxygen-carrying capacity of the blood and is an adverse marker in overt HF.10 The availability of systematic, multi-system measurements during routine surveillance in the Framingham Heart Study enabled comprehensive assessment of these varied non-cardiac organ systems in relation to incident HF in the community. Our findings regarding the association with renal impairment are consistent with the Health ABC Heart Failure Model for incident HF in the elderly.25 In contrast, we did not find a significant association with hypoalbuminemia, and this may be due to differences in study samples (larger proportion of blacks and lower baseline serum albumin in the Health ABC Study).

In aggregate, these results suggest that the manifestation of clinically overt HF may be hastened by subclinical dysfunction in multiple organ systems. This is likely to particularly affect elderly individuals who have age-related decline in multi-organ function or multiple non-cardiac co-morbidities. Recognizing the contribution of non-cardiac dysfunction to HF progression may carry important clinical implications for preventing and managing heart failure. Further studies are warranted to validate these findings in other populations, evaluate for potential effect modification by covariates such as sex, and assess the potential impact of treatment of these risk factors on the risk of future HF.

Association of non-cardiac dysfunction with HFREF versus HFPEF

The distinction between factors associated with incident HFREF versus HFPEF deserves comment. The association of renal dysfunction and anemia with the risk of HFREF are consistent with classic studies

of the cardiorenal syndrome and the known prognostic impact of anemia in overt HFREF.10 Interestingly, the most prominent non-cardiac predictor of incident HFPEF was airflow obstruction. This observation is supported by large epidemiologic studies showing a high prevalence of pulmonary disease in patients with HFPEF,26, 27 the frequent co-existence of HF in patients with chronic obstructive lung disease,28 as well as a recent study in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort demonstrating an association between airflow obstruction and abnormal LV filling.9 While this also raises the question of potential misdiagnosis of HFPEF, this is unlikely given the high specificity of the Framingham criteria for HF,29 the reliability of the diagnosis as demonstrated by consistent application of the same criteria over decades and stringent adjudication of endpoints in the Heart Study, and the lack of an alternative explanation for the clinical presentation (since the extent of pulmonary impairment was not severe enough to explain symptoms). Overall, the different predictors of HFREF versus HFPEF are consistent with prior epidemiologic,20 pathophysiologic,30 molecular,31 and outcome32 data supporting the notion that HFREF and HFPEF may represent separate entities. These observations may guide future clinical trial design, particularly in HFPEF where trials have, so far, been disappointing.

Strengths and limitations

The strengths of our study include the large community-based sample, uniform measurements of function of multiple organ systems, and longitudinal follow-up with continuous surveillance for, and careful validation of, HF outcomes. Further, the use of purely clinical criteria for the diagnosis of HF19 independent of LVEF is particularly advantageous in this setting. Limitations include the lack of tissue Doppler characterization of diastolic dysfunction, and the inherent pitfalls in using echocardiographic indices of diastolic filling as indicators of diastolic dysfunction. Nonetheless, mitral Doppler indices are widely available; and our results are consistent with previous studies using more comprehensive assessment of diastolic dysfunction.3, 24 We acknowledge the observational nature of our study which precludes conclusions regarding causality, as well as the modest effect sizes

for non-cardiac organ system variables and potential for residual confounding or effect modification by other factors. We did not use time-varying covariates, but speculate that organ dysfunction would worsen with aging in most individuals, leading to even stronger associations with incident HF. Our uniformly white sample limits the generalizability of our findings to other ethnicities, and independent validation in other cohorts is warranted.

Conclusions

Our prospective observations in a large, community-based sample demonstrate that antecedent subclinical cardiac and non-cardiac major organ system dysfunction are associated with increased risk of clinical HF. These findings contribute to the understanding of HF as a progressive disease syndrome, and underscore the potential importance of non-cardiac risk factors in predisposing to the manifestation of overt HF.

Acknowledgments.

Funding sources: National Heart, Lung and Blood Institute (Contract No. NO1-HC-25195). Dr. Lee was supported by a clinician-scientist award from the Canadian Institutes of Health Research.

Conflict of Interest Disclosures: None.

REFERENCES

1. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119:e391-479.
2. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2005;26:1115-1140.
3. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289:194-202.
4. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation. 2007;115:1982-1990.
5. Smith GL, Shlipak MG, Havranek EP, Foody JM, Masoudi FA, Rathore SS, Krumholz HM. Serum urea nitrogen, creatinine, and estimators of renal function: mortality in older patients with cardiovascular disease. Arch Intern Med. 2006;166:1134-1142.
6. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. Am Heart J. 2008;155:883-889.
7. Arques S, Ambrosi P, Gelisse R, Luccioni R, Habib G. Hypoalbuminemia in elderly patients with acute diastolic heart failure. J Am Coll Cardiol. 2003;42:712-716.
8. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail. 2009;11:130-139.
9. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, Jiang R, Kawut SM, Kronmal RA, Lima JA, Shahar E, Smith LJ, Watson KE. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med.362:217-227.
10. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL,

van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol. 2008;52:818-827.

11. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. JAMA. 1987;257:2318-2324.
12. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. JAMA. 2008;300:431-433.
13. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. Circ Heart Fail. 2008;1:91-97.
14. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation. 2003;108:977-982.
15. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health. 1951;41:279-281.
16. Sagie A, Benjamin EJ, Galderisi M, Larson MG, Evans JC, Fuller DL, Lehman B, Levy D. Reference values for Doppler indexes of left ventricular diastolic filling in the elderly. J Am Soc Echocardiogr. 1993;6:570-576.
17. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J. 2007;28:2539-2550.
18. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, Levy D. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA. 2002;288:1252-1259.
19. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971;285:1441-1446.
20. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation. 2009;119:3070-3077.
21. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med.
22. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer

S, Doring A, Broeckel U, Riegger G, Schunkert H. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J. 2003;24:320-328.

23. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study. J Am Coll Cardiol. 2001;37:1042-1048.
24. Correa de Sa DD, Hodge DO, Slusser JP, Redfield MM, Simari RD, Burnett JC, Chen HH. Progression of preclinical diastolic dysfunction to the development of symptoms. Heart.96:528-532.
25. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB. Incident heart failure prediction in the elderly: the health ABC heart failure score. Circ Heart Fail. 2008;1:125-133.
26. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. JAMA. 2006;296:2209-2216.
27. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol. 2006;47:76-84.
28. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, Hoes AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J. 2005;26:1887-1894.
29. Mosterd A, Deckers JW, Hoes AW, Nederpel A, Smeets A, Linker DT, Grobbee DE. Classification of heart failure in population based research: an assessment of six heart failure scores. Eur J Epidemiol. 1997;13:491-502.
30. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation. 2006;113:1966-1973.
31. Borbely A, Papp Z, Edes I, Paulus WJ. Molecular determinants of heart failure with normal left ventricular ejection fraction. Pharmacol Rep. 2009;61:139-145.
32. Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. Eur J Heart Fail. 2009;11:855-862.

Chapter 4

Understanding the predisposition of women to heart failure with preserved ejection fraction

4.1. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial.

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ABSTRACT

Background:
There are few sex-specific outcomes data in heart failure with preserved ejection fraction (HFPEF).

Methods and Results: We assessed sex differences in baseline characteristics and outcomes among 4128 patients with HFPEF in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Women (N=2491) with HFPEF were ~1 year older (72±7y vs 71±7y) and more likely to be obese (46 vs 35%), have chronic kidney disease (34 vs 26%) and hypertension (91 vs 85%) than men; but less likely to have an ischemic etiology (19 vs 34%), atrial fibrillation (27 vs 33%) or chronic obstructive pulmonary disease (8 vs 13%) (all $p<0.001$). Over a mean of 49.5 months, there were 881 deaths (447 in women, 434 in men; RR 0.64; 95%CI, 0.56-0.74) and 5776 hospitalizations (3239 in women, 2537 in men; RR 0.80; 95% CI, 0.76-0.84). Women had lower risk of all-cause events (deaths and hospitalizations), even after adjusting for baseline characteristics (adjusted HR 0.81; 95%CI, 0.73-0.89). However, the sex-related difference in risk of all-cause events was modified in the presence or absence of atrial fibrillation, renal dysfunction, stable angina pectoris or advanced New York Heart Association class symptoms.

Conclusions: In patients with typical HFPEF, there were prominent sex differences in baseline characteristics and outcomes. Women had better overall prognosis, although the presence of four common baseline characteristics appeared to moderate this finding.

Clinical Trial Registration: URL - http://www.clinicaltrials.gov. Unique identifier - NCT000095238.

INTRODUCTION

Epidemiological studies have revealed striking sex-related differences in clinical presentation,1-5 risk factors6, 7 and prognosis8-10 of heart failure (HF). One of the most notable sex-related differences in HF is that most women have HF with preserved ejection fraction (HFPEF), an important disorder that is incompletely understood.11

Previous studies have been limited by retrospective design,12 under-representation of women, or exclusion of HFPEF.13 Three previous trials (DIG-PEF,14 CHARM-Preserved,15 PEP-CHF16) have included sizeable numbers of patients with HFPEF but have been criticized for selecting patients who were not necessarily representative of patients with HFPEF seen in population-based studies.17 The I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial18 is the largest HFPEF trial to date and included patients (60% women) that closely resembled those with typical HFPEF described in population-based epidemiologic studies.1, 2

Elucidating the effect of sex and risk factors on outcomes in HFPEF may advance fundamental understanding of the HFPEF syndrome and guide the design of tailored intervention strategies. Recognizing that a substantial proportion of events during follow-up in the I-PRESERVE trial were non-cardiovascular events,19 in sharp contrast to the profile of events observed in HF studies of predominantly younger men, we hypothesized that women with HFPEF would be older and would have more non-cardiovascular co-morbidities at baseline compared to men, which could predispose to sex-related differences in outcomes in HFPEF. Accordingly, we aimed to test this hypothesis by examining the differences in clinical characteristics and prognosis in women and men with HFPEF from the large, prospective I-PRESERVE trial.

METHODS

Sample

The study sample consisted of the 4128 patients enrolled in the I-PRESERVE trial.18 Inclusion criteria included age ≥60 years old, clinical signs and symptoms of HF and a left ventricular ejection fraction ≥45%. The intervention was irbesartan 300 mg/d versus placebo.

Although the primary trial results,18 mode of death19 and HF–related quality of life20 have been previously published, where some results were stratified by sex and heterogeneity in the treatment effect by sex was not found, the detailed sex-specific analyses and hospitalization events presented here have not been previously reported.

Outcomes

The primary outcome in I-PRESERVE was a composite of all-cause death or the first hospitalization for a protocol-specified adjudicated cardiovascular hospitalization (defined as worsening HF, unstable angina, myocardial infarction, ventricular arrhythmia, atrial arrhythmia or stroke). Secondary outcomes included cardiovascular death, all-cause mortality, HF mortality or hospitalization, and change in quality of life related to heart failure, NYHA functional class, and N-terminal pro B-type natriuretic peptide (NT-proBNP) level in blood (Roche Elecsys assay®). Outcomes (deaths and hospitalizations) were adjudicated by an independent Clinical End Point Committee using pre-specified criteria that have been previously published.19 HF mortality was defined as death due to worsening or intractable HF, while HF hospitalization was defined as one with a primary diagnosis of worsening HF, where patients with worsening HF displayed symptoms and signs of HF as well as diagnostic evidence such as a significant increase in natriuretic peptides, radiographic congestion or prerenal azotemia.

Statistical analysis

Baseline variables were compared between men and women using two-sided Student t tests or Wilcoxon rank-sum tests for continuous variables, and Fisher exact tests or chi-square tests for categorical variables. For each outcome of interest, time to first event was recorded, while other events were censored. Cox proportional hazards analysis was used to model the effect of sex, baseline covariates (age, obesity, NHYA status, HF etiology, HF hospitalization 6 months prior to baseline, history of hypertension, stable angina pectoris, myocardial infarction, percutaneous coronary intervention/ coronary artery bypass surgery, atrial fibrillation, diabetes mellitus, stroke/transient ischemic attack, chronic obstructive pulmonary disease/asthma, valve

disease, smoking, ejection fraction, heart rate, systolic blood pressure, hemoglobin, NTproBNP, neutrophil count, glomerular filtration rate, and medications), as well as the interactions between sex and each baseline covariate. The analyses of interactions with sex focused on all-cause events because the results for cardiovascular and non-cardiovascular events were similar, there were more all-cause events, and competing risks are incorporated into the endpoint. To help account for multiple comparisons, the threshold for statistical significance was $P<0.01$. Estimated P-values are presented for readers who would like to make further adjustments considering the number of tests done to compare women and men.

RESULTS

Baseline characteristics

Among 4128 elderly patients with HFPEF, 2491 (60%) were women, who were, on average, 1 year older than men (Table 1). Compared to men, women were: more likely to be obese and have a history of hypertension; less likely to have an ischemic etiology, stable angina pectoris, previous myocardial infarction, atrial fibrillation, chronic obstructive pulmonary disease or smoking; and had a similar prevalence of diabetes mellitus. At baseline in women compared to men, heart rate was higher and peripheral edema was more prevalent. HF-specific quality of life was worse in women compared to men. Women were more likely than men to have chronic kidney disease, but less likely to be anemic (using differential hemoglobin cutpoints) and had lower NT-proBNP levels.

Association between sex and outcomes

In time to first event (death or hospitalization) analyses, there were 2430 all-cause events over a mean follow-up of 49.5 months, of which 1754 were of cardiovascular causes (Table 2, Figure 1). Women had a 21% lower unadjusted risk of all-cause events than men which persisted after adjusting for the differences in baseline characteristics. As with all-cause events, the unadjusted risk of the primary outcome of I-PRESERVE (all-cause death or hospitalization for protocol-specified cardiovascular causes) was 28% lower in women than men,

remaining significant (albeit attenuated) after adjusting for baseline covariates. Similarly, in women compared to men the unadjusted risk of cardiovascular events alone was 25% lower, and the unadjusted risk of non-cardiovascular events 19% lower, with the difference remaining significant even after adjusting for baseline covariates. There was a trend for lower risk of HF-specific events in women than men that did not reach statistical significance. For all-cause mortality, there were a total of 881 deaths (447 [17.9%] in women, 434 [26.5%] in men; unadjusted HR 0.64; 95% CI, 0.56-0.73).

Table 3 shows the total events in women and men. In both women and men with HFPEF, there were more deaths from cardiovascular than non-cardiovascular causes, with the most common cardiovascular cause of death being sudden death. Non-cardiovascular causes comprised 29.1% of all deaths in women, and 31.8% of all deaths in men. There were a total of 5776 all-cause hospitalizations (including repeat admissions; 3239 in women and 2537 in men). In both women and men, there were more hospitalizations for cardiovascular than non-cardiovascular causes, with the most common cardiovascular cause of hospitalization being worsening HF. Non-cardiovascular causes comprised 45.1% of hospitalizations in women, and 44.5% of hospitalizations in men. The risk ratio for overall hospitalizations in women vs men was 0.80 (95% CI, 0.76-0.84). For cardiovascular and non-cardiovascular hospitalizations, risk was similarly lower in women, with risk ratios of 0.81 (0.75-0.87) and 0.78 (0.73-0.86) respectively. Virtually all hospitalization subcategories were also lower in women than men.

Sex-differences in the Predictors of All-cause Events

In sex-stratified multivariable analyses including all baseline covariates, variables associated with all-cause events in both men and women included higher age, HF hospitalization within 6 months, history of chronic obstructive pulmonary disease, lower hemoglobin and higher NT-proBNP (Table 4). In women, obesity, diabetes mellitus, lower glomerular filtration rate and antiarrythmic medications were also significantly associated with higher risk of all-cause events. In men, higher NYHA status (class III/IV versus I/II), a history of coronary

Table 1. Baseline clinical characteristics by sex

Characteristic	Women (N=2491)	Men (n=1637)	*P* value
Clinical			
Age, years	72 ± 7	71 ± 7	<0.001
Body mass index, kg/m^2	30 ± 6	29 ± 5	<0.001
Obesity* (%)	46	35	<0.001
Heart failure etiology (% ischemic)	19	34	<0.001
Stable angina pectoris(%)	38	43	<0.001
Myocardial infarction (%)	17	33	<0.001
PCI/CABG (%)	9	20	<0.001
Hypertension (%)	91	85	<0.001
Atrial fibrillation (%)	27	33	<0.001
Diabetes mellitus (%)	28	27	0.74
Chronic obstructive pulmonary disease (%)	8	13	<0.001
Smoking (%)	9	32	<0.001
NYHA class II/III/IV (%)	20/77/2	22/75/3	0.006
Hospitalization in the last 6 months (%)	44	45	0.49
Ejection fraction %	61 ± 9	58 ± 9	<0.001
Physical examination			
Heart rate, bpm	72 ±11	71 ±10	0.003
Systolic blood pressure, mmHg	137 ±15	136 ± 15	0.14
Diastolic blood pressure, mmHg	79 ± 9	79 ± 9	0.80
S3 gallop, number (%)	8	9	0.10
Jugular venous distension (%)	7	10	0.008
Hepatomegaly (%)	17	20	0.16
Edema (%)	25	21	0.002
Rales (%)	25	24	0.43
Quality of life			
Minnesota living with heart failure score	45 ± 21	39 ± 21	<0.001
Investigations			
Radiologic pulmonary congestion (%)	42	40	0.001
Median (Q1-Q3) NT-proBNP, pg/mL	301 (126-897)	413 (155-1051)	<0.001
Hemoglobin, g/dL	13.5 ± 1.8	14.5 ± 1.9	<0.001
Anemia† (%)	11	16	<0.001
Estimated glomerular filtration rate, ml/min/1.73m^2	70.8 ± 22.1	75.2 ± 22.9	<0.001
Chronic kidney disease‡ (%)	34	26	<0.001
Potassium, µmol/L	4.4 ± 0.5	4.5 ± 0.5	0.10
Medications			
Loop diuretic (%)	51	53	0.08
Thiazide diuretic(%)	41	34	<0.001
Spironolactone(%)	15	17	0.08
Angiotensin converting enzyme inhibitor(%)	23	29	<0.001
Digoxin(%)	12	16	0.006
Beta-blocker(%)	59	59	0.93
Antiarrythmic(%)	8	11	0.003
Calcium channel blocker(%)	42	37	<0.001
Nitrate(%)	25	30	<0.001
Oral anticoagulant(%)	55	64	<0.001
Aspirin(%)	52	59	<0.001
Lipid lowering (%)	28	35	<0.001

Data are mean ± SD

*Obesity defined as body mass index ≥ 30 kg/m2

†Anemia defined as hemoglobin ≤ 13 g/dL in men and ≤ 12 g/dL in women

‡Chronic kidney disease defined as estimated glomerular filtration rate <60 ml/min/1.73m2

PCI/CABG, percutaneous coronary intervention/ coronary artery bypass surgery; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Table 2. Association between sex and time to first outcomes

Outcome	Number of events			Event rate per 100 patient-years		Univariable Analysis		Multivariable Analysis*	
	All Patients	Women	Men	Women	Men	HR (95%CI) Women vs Men	*P* value	HR (95%CI) Women vs Men	*P* value
Primary outcome of I-PRESERVE †	1505	812	693	8.93	12.49	0.72 (0.65-0.80)	<0.001	0.79 (0.70-0.91)	0.001
All-cause death	881	447	434	4.32	6.72	0.64 (0.56-0.73)	<0.001	0.70 (0.59-0.83)	<0.001
All-cause hospitalization or death	2430	1382	1049	19.42	25.05	0.79 (0.73-0.86)	<0.001	0.80 (0.72-0.89)	<0.001
Cardiovascular hospitalization or death	1754	970	784	11.76	15.97	0.75 (0.68-0.83)	<0.001	0.81 (0.72-0.92)	0.001
Non-cardiovascular hospitalization or death	1483	846	638	9.89	12.40	0.81 (0.72-0.89)	<0.001	0.78 (0.69-0.90)	<0.001
Heart failure hospitalization or death	716	420	296	4.43	5.02	0.89 (0.77-1.04)	0.140	0.94 (0.77-1.14)	0.51
First all-cause hospitalization	2278	1314	964	18.43	23.14	0.82 (0.75-0.88)	<0.001	0.77 (0.66-0.89)	<0.001

* Adjusted for age, obesity, NHYA status, HF etiology, HF hospitalization within 6 months, co-morbidities/ risk factors (history of hypertension, stable angina, myocardial infarction, PCI/CABG, atrial fibrillation, diabetes, stroke/TIA, COPD/asthma, valve disease, smoking), ejection fraction capped at 60%, heart rate, systolic blood pressure, hemoglobin, ln-NTproBNP, ln-neutrophil count, glomerular filtration rate capped at 90ml/mim/1.73m2, and all medications. † Death from any cause or hospitalization for protocol-specified cardiovascular cause (heart failure, myocardial infarction, arrhythmia, or stroke)

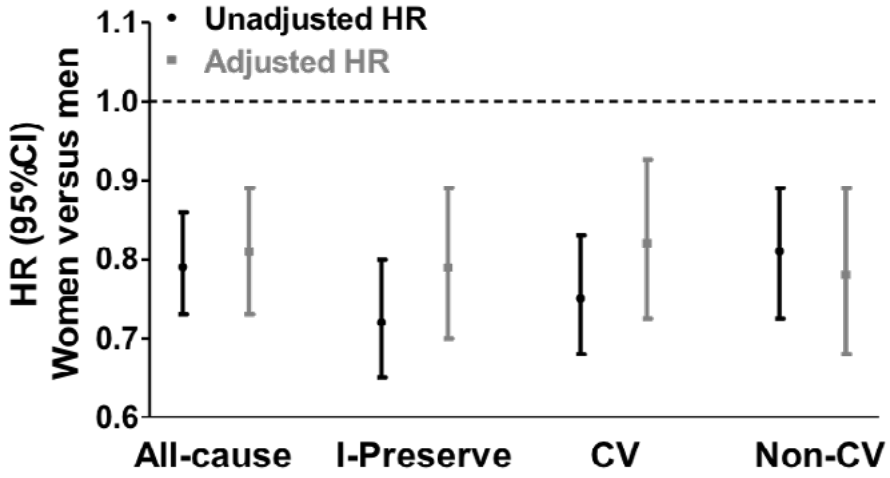

Figure 1. Association between sex and time to first event. Hazards ratios (HRs) for women versus men for first events where HR<1 indicates lower risk in women. Event categories include: All Cause (all-cause death or hospitalization); I-PRESERVE (the primary outcome of the I-PRESERVE trial, which was all-cause death or hospitalization for protocol-specified cardiovascular cause including heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke); CV (cardiovascular events); and Non-CV (non-cardiovascular events). Black circles and lines represent unadjusted HR and 95% confidence intervals (95%CI). Gray squares and lines represent HR and 95%CI adjusted for age, obesity, New York Heart Association status, HF etiology, HF hospitalization within 6 months, co-morbidities/ risk factors (history of hypertension, stable angina pectoris, myocardial infarction, percutaneous coronary intervention/ coronary artery bypass surgery, atrial fibrillation, diabetes, stroke/transient ischemic attack, chronic obstructive lung disease, valve disease, smoking), ejection fraction, heart rate, systolic blood pressure, hemoglobin, N-terminal pro-B-type natriuretic peptide, neutrophil count, glomerular filtration rate, and medications.

revascularization, higher neutrophil count and smoking were also significantly associated with higher risk of all-cause events.

In order to gain further insights into the HR for all-cause events in women relative to men, we tested for interactions between sex and baseline variables. There were significant interactions between sex and 4 baseline characteristics: stable angina pectoris, atrial fibrillation, NYHA class and eGFR (Table 4 last column). The effect of each interaction, analyzed one at a time, is shown in Figure 2A. The risk of all-cause events was not lower in women in the presence of atrial fibrillation or

Table 3. Total mortality and hospitalizations and causes in women and men

Events	Numbers (%) events*		Event rate per 100 patient-years of follow-up†		Risk Ratio (95% CI)	P-value
	Women (n=2491)	Men (n=1637)	Women	Men		
Deaths						
All-cause deaths	447	434	4.32	6.72	0.64 (0.56-0.74)	<0.0001
Non-cardiovascular deaths	130 (29.1)	138 (31.8)	1.26	2.14	0.59 (0.46-0.75)	<0.0001
Cardiovascular deaths	260 (58.2)	272 (62.7)	2.51	4.21	0.60 (0.50-0.71)	<0.0001
Sudden death	104 (23.3)	127 (29.3)	1.01	1.97	0.51 (0.39-0.67)	<0.0001
Pump failure	62 (13.9)	63 (14.5)	0.6	0.98	0.61 (0.43-0.89)	0.007
Stroke	45 (10.1)	31 (7.1)	0.44	0.48	0.91 (0.56-1.48)	0.67
Myocardial infarction	23 (5.1)	22 (5.1)	0.22	0.34	0.65 (0.34-1.23)	0.16
Other vascular death	17 (3.8)	15 (3.5)	0.16	0.23	0.70 (0.33-1.52)	0.33
Other cardiac death	9 (2.0)	14 (3.2)	0.09	0.22	0.40 (0.15-0.99)	0.033
Unknown/ unclassified deaths	57 (12.8)	24 (5.5)	0.55	0.37	1.48 (0.91-2.50)	0.1
Hospitalizations						
All-cause hospitalizations	3239	2537	31.33	39.29	0.80 (0.76-0.84)	<0.0001
Non-cardiovascular hospitalizations	1462 (45.1)	1130 (44.5)	14.1	17.5	0.81 (0.75-0.87)	<0.0001
Cardiovascular hospitalizations	1761 (54.4)	1407 (55.5)	17.0	21.8	0.78 (0.73-0.86)	<0.0001
Worsening heart failure	736 (22.7)	506 (19.9)	7.1	7.8	0.91 (0.81-1.02)	0.098
Cardiovascular procedure	147 (4.5)	182 (7.2)	1.42	2.81	0.50 (0.40-0.63)	<0.0001
Unstable angina/MI	196 (6.1)	162 (6.4)	1.90	2.50	0.76 (0.61-0.94)	0.009
Arrhythmia	166 (5.1)	117 (4.6)	1.61	1.81	0.89 (0.70-1.13)	0.32
Chest pain	131 (4.0)	122 (4.8)	1.27	1.89	0.67 (0.52-0.87)	0.002
Stroke/ transient ischemic attack	126 (3.9)	105 (4.1)	1.22	1.63	0.75 (0.57-0.98)	0.03
Other cardiac	79 (2.4)	53 (2.1)	0.76	0.82	0.93 (0.65-1.34)	0.68
Peripheral vascular disease	59 (1.8)	57 (2.2)	0.57	0.88	0.65 (0.44-0.95)	0.02
Syncope	42 (1.3)	61 (2.4)	0.41	0.94	0.43 (0.28-0.65)	<0.0001
Hypertension	58 (1.8)	16 (0.6)	0.56	0.25	2.26 (1.28-4.22)	0.002
Hypotension	19 (0.6)	19 (0.7)	0.18	0.29	0.62 (0.31-1.25)	0.15
Sudden death	2 (0.1)	1 (<0.1)	0.02	0.015	1.25 (0.07-73.7)	0.9

*Numbers represent absolute numbers of events (% of total events in women and men), including multiple hospitalizations per patient

†Numbers represent rates of death and first admission to hospital for specified causes per 100 patient-years of follow-up

renal dysfunction, and in the absence of advanced NYHA class III/IV symptoms or stable angina pectoris. To show how the women-to-men all-cause HR's varied with all four interacting variables, we entered different values of the interacting variables into the estimated Cox regression model as shown in Figure 2B. There was also a significant interaction between sex and antiarrythmic medications, but numbers were too small for further analyses.

DISCUSSION

In this large sample of women and men with HFPEF, there were notable sex-related differences in baseline risk factors. Women were more likely to be obese and have a history of hypertension or renal impairment, while only ~1 year older than men. Men were more likely to have an ischemic etiology for HFPEF, atrial fibrillation, chronic obstructive pulmonary disease and anemia. Even accounting for these baseline differences, women with HFPEF were ~20% less likely than men to experience death or hospitalization for any cause during follow-up. A lower risk was observed for women for both cardiovascular and non-cardiovascular events. This lower relative risk for women could not be explained by adjustment for differences in baseline characteristics. However, the sex-related difference in risk of all-cause events was modified by atrial fibrillation, stable angina pectoris, NYHA class, and renal function.

Prior reports from HF trials that examined sex differences were largely limited to HF with reduced ejection fraction and included relatively small numbers of women.13 I-PRESERVE was the largest prospective trial of HFPEF to date and the first in which women were a majority of the patients, reflecting its prevalence in the population. The number of women in I-PRESERVE (n=2491) was more than twice that of CHARM-Preserved, the largest previously reported trial of HFPEF. Further, the baseline characteristics the I-PRESERVE patients closely resembled those with HFPEF described in population based studies.1, 2 In contrast, in CHARM-Preserved there was a dominance of men, coronary artery disease, and relatively low mean ejection fraction in patients who were, on average, younger than those seen in population and community studies. This was also the case for the report from the

Table 4. Sex differences in the multivariable predictors of all-cause events

Variable	HR (95%CI); P value		P-value
	Women	Men	Interaction
Age	1.024 (1.014-1.035); P<0.001	1.025 (1.013-1.037); P<0.001	0.45
Obesity	1.210 (1.063-1.377); P=0.004	1.136 (0.969-1.330); P=0.115	0.52
NYHA (class III/IV vs I/II)	1.019 (0.852-1.220); P=0.835	1.329 (1.076-1.640); P=0.008	0.006
HF etiology (ischemic vs non-ischemic)	1.046 (0.868-1.262); P=0.635	1.159 (0.956-1.406); P=0.134	0.054
Hypertension	0.845 (0.677-1.055); P=0.138	0.999 (0.813-1.228); P=0.990	0.41
Stable angina pectoris	1.020 (0.880-1.182); P=0.795	1.117 (0.947-1.317); P=0.191	0.007
Myocardial infarction	1.035 (0.859-1.247); P=0.718	1.040 (0.867-1.248); P=0.669	0.13
PCI/CABG	1.107 (0.870-1.408); P=0.408	1.242 (1.011-1.525); P=0.039	0.96
Atrial fibrillation	1.115 (0.928-1.341); P=0.244	0.834 (0.680-1.022); P=0.080	0.005
Diabetes mellitus	1.454 (1.128-1.872); P=0.004	1.178 (0.851-1.631); P=0.323	0.49
Smoking	1.117 (0.905-1.378); P=0.301	1.208 (1.035-1.410); P=0.016	0.58
Chronic obstructive lung disease	1.351 (1.081-1.689); P=0.008	1.301 (1.054-1.606); P=0.014	0.59
Valve disease	1.117 (0.925-1.349); P=0.248	1.140 (0.909-1.431); P=0.257	0.47
Heart rate (per 1 bpm)	1.004 (0.998-1.010); P=0.247	1.004 (0.996-1.011); P=0.336	0.97
SBP (per 1 mmHg)	1.000 (0.996-1.005); P=0.889	1.000 (0.995-1.005); P=0.917	0.90
Hemoglobin (per 1 g/dL)	0.962 (0.929-0.996); P=0.029	0.946 (0.912-0.982); P=0.003	0.95
NT-proBNP (per 1 log unit)	1.172 (1.085-1.265); P<0.001	1.174 (1.077-1.281); P=<0.001	0.44
Hospitalization in 6 months	1.447 (1.240-1.690); P<0.001	1.411 (1.171-1.700); P<0.001	0.049
Neutrophil count (per 1 log unit)	1.154 (0.966-1.377); P=0.114	1.634 (1.309-2.041); P<0.001	0.048
Ejection Fraction	0.985 (0.972-0.999); P=0.033	0.992 (0.977-1.007); P=0.281	0.70
eGFR (per 1 ml/min/1.73 m^2)	0.991 (0.987-0.994); P<0.001	0.997 (0.993-1.002); P=0.211	0.01
Antiarrythmic	1.320 (1.052-1.656) P=0.016	1.036 (0.806-1.333) P=0.781	0.004

NYHA, New York Heart Association; HF, heart failure; PCI/CABG, percutaneous coronary intervention/ coronary artery bypass surgery; SBP, systolic blood pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate

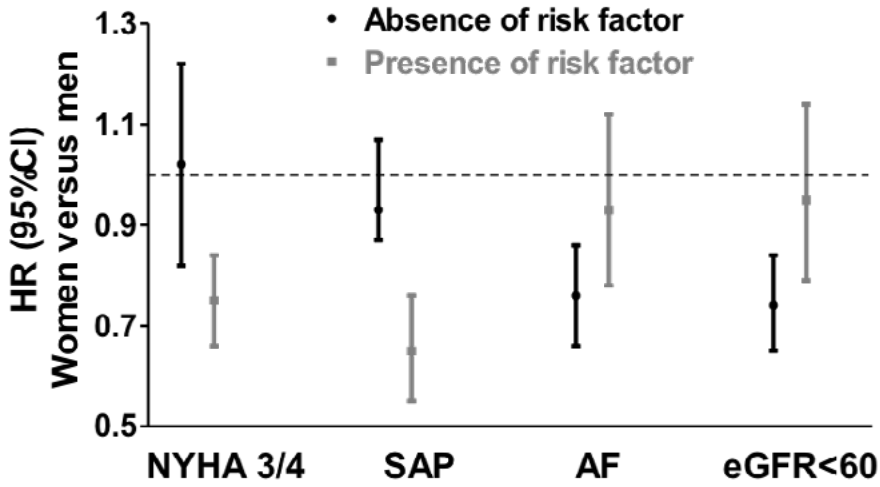

Figure 2. Effect of interactions on association between sex and all-cause events. The y-axis indicates hazards ratios (HRs) for women versus men for all-cause events where HR<1 indicates lower risk in women. A) Results of univariable analyses showing the HRs in the absence (black) or presence (gray) of specific risk factors, including New York Heart Association (NYHA) class 3 or 4, stable angina pectoris (SAP), atrial fibrillation (AF); and reduced estimated glomerular filtration rate (eGFR). B) Results of multivariable analyses accounting for all four significant interactions and adjusting for age, obesity, New York Heart Association status, HF etiology, HF hospitalization within 6 months, co-morbidities/ risk factors (history of hypertension, stable angina pectoris, myocardial infarction, percutaneous coronary intervention/ coronary artery bypass surgery, atrial fibrillation, diabetes, stroke/transient ischemic attack, chronic obstructive lung disease, valve disease, smoking), ejection fraction, heart rate, systolic blood pressure, hemoglobin, N-terminal pro-B-type natriuretic peptide, neutrophil count, glomerular filtration rate, and medications. The graph indicates situations where specific risk factors are present (cross) or absent (tick), at levels of estimated glomerular filtration rate (eGFR) of 70 ml/min/1.73 m2 (black circles), 60 ml/min/1.73 m2 (gray squares), and 50 ml/min/1.73 m2 (black triangles).

earlier DIG trial.14

These are important considerations since age, sex, co-morbidities and outcomes are closely related in HF: women with HF tend to be older than men with HF, leading to the speculation that women with HFPEF, being older, would have more non-cardiovascular co-morbidities, thus predisposing them to a higher rate of non-cardiovascular events than men.21 Our findings are contrary to this hypothesis. In this sample, the age distributions were similar between

women and men with HFPEF, and the risk of non-cardiovascular events was lower in women, even when adjustments were made for several significant sex differences in the baseline characteristics. It is notable that non-cardiovascular events were common (although cardiovascular events predominated), with approximately 30% of all deaths and 45% of hospitalizations due to non-cardiovascular causes. These rates of non-cardiovascular outcomes are similar to those reported from population-based studies and Medicare claims data in HFPEF,21-26 and far exceed the rates of non-cardiovascular events typically seen in patients with HF with reduced ejection fraction where men predominate.27

Our analyses of I-PRESERVE data indicate that among elderly patients with HFPEF, women in general had a lower risk of adverse clinical events than men. These results are consistent with previous reports including the recently published Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC) meta-analysis,28 where women with HF were shown to have lower all-cause mortality over three years than men, irrespective of EF and even after accounting for baseline differences in risk factors. Similarly in the overall CHARM Program, first cardiovascular events were lower in women than men regardless of ejection fraction. However, our results differ from CHARM as all-cause and non-cardiovascular hospitalization risks for women were also lower than in men in our cohort. Sex-specific data in HFPEF alone from CHARM-Preserved were displayed but were not analyzed in depth,29 and the estimated sex-specific event rates did not appear to be lower in women. Of note, unlike in CHARM-Preserved, we used the composite endpoint of death or hospitalization. We therefore extend the previously published data by showing that the lower risk in women than men with typical HFPEF persisted using composite outcomes for mortality as well as hospitalizations, and was observed not only for first events but also for multiple all-cause, cardiovascular, and non-cardiovascular events experienced throughout the entire 49 month period of follow-up.

We further examined whether the relative risk in women versus men depended on the values of specific baseline characteristics. Atrial fibrillation and renal dysfunction appeared to carry greater risk

in women than men. Previous studies have shown that women are more likely than men to experience symptomatic episodes of atrial fibrillation, higher heart rates during episodes, and a higher frequency of recurrences.30 While further research is needed to understand these sex differences in risk, potential reasons may include the lower rate of treatment with statins31 or the higher rate of obesity among women compared to men in our cohort, both of which may predispose women to more severe arrhythmic episodes (though not necessarily greater prevalence of disease). The coexistence of renal dysfunction in HFPEF is common, but poorly understood and often under-diagnosed.32 Despite recognition of renal dysfunction as an important predictor of outcomes in HFPEF among women,33 the sex difference in the extent of risk imparted by similar degrees of renal dysfunction has not been widely appreciated previously. The differential impact of symptoms of angina and HF on women versus men may relate to known difficulties of interpreting symptoms of ischemic heart disease in women, which are more often atypical in women than men, or differences in perception of symptoms between women and men. Although these data extend previous reports, we agree with other commentators28 that there remains uncertainty regarding the interaction between HF etiology and sex-related outcomes, as well as the need for further studies to understand this relationship.

Limitations

Our study was performed in the context of a clinical trial, which may limit the generalizeability of our findings. However, the I-PRESERVE cohort at baseline closely resembled the patients with typical HFPEF described in population-based epidemiologic studies.1, 2 Furthermore, I-PRESERVE had the largest group of women with HFPEF in a prospective study of HFPEF and included detailed characterization, systematic long-term follow-up, and adjudication of outcomes. As in all studies, we cannot definitively exclude that some of the outcomes that appeared to be sex-related were instead due to other unmeasured factors or to chance given the number of comparisons. Thus, these results should be interpreted with caution and confirmed in future studies.

Conclusion

There were several sex differences in elderly patients with typical HFPEF in I-PRESERVE. Women had better overall prognosis than men and were at lower risk of both cardiovascular and non-cardiovascular events, although this effect was modified by the presence or absence of atrial fibrillation, renal dysfunction, stable angina pectoris or advanced NYHA class symptoms. Further research is needed to understand the complex sex-related differences in risk among HF patients. A better understanding of sex-specific risk factors may help inform strategies aimed at improving outcomes in this important disorder.

Sources of funding:

The I-PRESERVE trial was funded by Bristol-Myers Squibb and Sanofi-Aventis, as was the present subanalysis. Also supported in part by NIH grants 37AG18915 and P30AG21222 (Dalane W. Kitzman).

Conflicts of interest/Disclosures:

The following authors served as consultants and received honoraria from Bristol-Myers Squibb for their roles in conducting the I-PRESERVE trial, including serving on the Coordinating Committee, Executive Committee, and / or Endpoint Committee: Dalane W. Kitzman, Michael R. Zile, Barry Massie, and Peter E Carson, Inder S. Anand, John J. McMurray, Robert S. McKelvie. Michel Komajda has received fees as member of the executive committee of the I PRESERVE trial

REFERENCES

1. Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol. 2001;87:413-419
2. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33:1948-1955
3. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: The Strong Heart Study. Am J Cardiol. 2000;86:1090-1096
4. Kupari M, Lindroos M, Iivanainen AM, Heikkila J, Tilvis R. Congestive heart failure in old age: Prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med. 1997;241:387-394
5. Masoudi FA, Havranek EP, Smith G, Fish RH, Steiner JF, Ordin DL, Krumholz HM. Gender, age, and heart failure with preserved left ventricular systolic function. J Am Coll Cardiol. 2003;41:217-223
6. Galvao M, Kalman J, DeMarco T, Fonarow GC, Galvin C, Ghali JK, Moskowitz RM. Gender differences in in-hospital management and outcomes in patients with decompensated heart failure: Analysis from the acute decompensated heart failure national registry (ADHERE). J Card Fail. 2006;12:100-107
7. Nieminen MS, Harjola VP, Hochadel M, Drexler H, Komajda M, Brutsaert D, Dickstein K, Ponikowski P, Tavazzi L, Follath F, Lopez-Sendon JL. Gender related differences in patients presenting with acute heart failure. Results from Euroheart Failure Survey II. Eur J Heart Fail. 2008;10:140-148
8. Deswal A, Bozkurt B. Comparison of morbidity in women versus men with heart failure and preserved ejection fraction. Am J Cardiol. 2006;97:1228-1231
9. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292:344-350
10. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397-1402
11. Kitzman DW. Diastolic dysfunction: One piece of the heart failure with normal ejection fraction puzzle. Circulation. 2008;117:2044-2046

12. Jessup M, Pina IL. Is it important to examine gender differences in the epidemiology and outcome of severe heart failure? J Thorac Cardiovasc Surg. 2004;127:1247-1252
13. Petrie MC, Dawson NF, Murdoch DR, Davie AP, McMurray JJ. Failure of women's hearts. Circulation. 1999;99:2334-2341
14. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Jr., Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: The Ancillary Digitalis Investigation Group trial. Circulation. 2006;114:397-403
15. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved trial. Lancet. 2003;362:777-781
16. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27:2338-2345
17. Tomoda H. Irbesartan for heart failure with preserved ejection fraction. New Engl J Med. 2009;360:1257-1258; author reply 1258-1259
18. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456-2467
19. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE. Mode of death in patients with heart failure and a preserved ejection fraction: Results from the irbesartan in heart failure with preserved ejection fraction study (I-PRESERVE) trial. Circulation. 2010;121:1393-1405
20. Rector TS, Carson PE, Anand IS, McMurray JJ, Zile MR, McKelvie RS, Komajda M, Kuskowski M, Massie BM. Assessment of long-term effects of irbesartan on heart failure with preserved ejection fraction as measured by the minnesota living with heart failure questionnaire in the irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial. Circ Heart Fail. 2012;5:217-225
21. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012;59:998-1005
22. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: A community perspective. Circ Heart Fail. 2008;1:91-97

23. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among medicare beneficiaries. Arch Intern Med. 1997;157:99-104
24. Grigorian-Shamagian L, Otero Ravina F, Abu Assi E, Vidal Perez R, Teijeira-Fernandez E, Varela Roman A, Moreira Sayagues L, Gonzalez-Juanatey JR. Why and when do patients with heart failure and normal left ventricular ejection fraction die? Analysis of >600 deaths in a community long-term study. Am Heart J. 2008;156:1184-1190
25. Curtis JP, Sokol SI, Wang Y, Rathore SS, Ko DT, Jadbabaie F, Portnay EL, Marshalko SJ, Radford MJ, Krumholz HM. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol. 2003;42:736-742
26. Muzzarelli S, Leibundgut G, Maeder MT, Rickli H, Handschin R, Gutmann M, Jeker U, Buser P, Pfisterer M, Brunner-La Rocca HP. Predictors of early readmission or death in elderly patients with heart failure. American heart journal. 2010;160:308-314
27. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The solvd investigators. New Engl J Med. 1991;325:293-302
28. Martinez-Selles M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, McMurray JJ, Swedberg K, Kober L, Berry C, Squire I. Gender and survival in patients with heart failure: Interactions with diabetes and aetiology. Results from the maggic individual patient meta-analysis. Eur J Heart Fail. 2012;14:473-479
29. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Pina IL, Granger CB, Ostergren J, Michelson EL, Solomon SD, Pocock S, Yusuf S, Swedberg K, Pfeffer MA. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: Results of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (charm) program. Circulation. 2007;115:3111-3120
30. Volgman AS, Manankil MF, Mookherjee D, Trohman RG. Women with atrial fibrillation: Greater risk, less attention. Gend Med. 2009;6:419-432
31. Amar D, Zhang H, Heerdt PM, Park B, Fleisher M, Thaler HT. Statin use is associated with a reduction in atrial fibrillation after noncardiac thoracic surgery independent of c-reactive protein. Chest. 2005;128:3421-3427
32. Lazzeri C, Valente S, Tarquini R, Gensini GF. Cardiorenal syndrome caused by heart failure with preserved ejection fraction. Int J Nephrol. 2011;2011:634903
33. Bibbins-Domingo K, Lin F, Vittinghoff E, Barrett-Connor E, Grady D, Shlipak MG. Renal insufficiency as an independent predictor of mortality among women with heart failure. J Am Coll Cardiol. 2004;44:1593-1600

Chapter 4

Understanding the predisposition of women to heart failure with preserved ejection fraction

4.2. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction.

Eur J Heart Fail. 2014 May;16(5):535-42

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Introduction

Heart failure with preserved ejection fraction (HFpEF) represents an important health problem due to its increasing prevalence and related morbidity, mortality, and cost to health care systems.1 In contrast to heart failure with reduced ejection fraction (HFrEF), there is no proven therapy to improve survival in HFpEF syndrome.

One of the most striking contrasts between HFpEF and HFrEF is the difference in sex prevalence, where women outnumber men by almost 2:1 in HFpEF,2 whereas men outnumber women in HFrEF. This may in part be explained by differences in the impact of aging and comorbidities on cardiovascular structure and function by sex.3 In the general population, aging is associated with more concentric remodeling, diastolic dysfunction, and vascular stiffness in women compared to men.4-5678910 However there are limited data about sex differences in cardiovascular structure and function in the setting of HFpEF.11,12

The PARAMOUNT trial prospectively compared the efficacy of therapy with an angiotensin receptor neprilysin inhibitor (ARNi) versus angiotensin receptor blocker (ARB) in patients with HFpEF (left ventricular ejection fraction ³ 45%, NT-proBNP at study entry > 400 pg/ml). In this population we aimed to assess differences in baseline clinical characteristics and cardiovascular structure and function between women and men.

Methods

Patient population

The design, baseline findings, and primary results of the Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial have been previously reported.13 Briefly, the study enrolled 301 patients with HFpEF, aged 40 years or older, with a left ventricular ejection fraction (LVEF) ³ 45%, and elevated NT-proBNP (> 400 pg/ml), while on active diuretic therapy. The main exclusion criteria included dyspnea due to non cardiac causes, significant valvular heart disease and estimated glomerular filtration rate (eGFR) lower than 30 ml/min*1.73 m2. The proportion of

patients enrolled with atrial fibrillation was limited to roughly 25% of the study population. Of the 301 patients randomized, 279 (93%) subjects had analyzable baseline echocardiographic data and were included in this analysis.

Echocardiography

All echocardiograms were analyzed in the cardiovascular imaging core laboratory at Brigham and Women's Hospital, Boston MA, USA. All measurements were made in triplicate in accordance with the recommendations of the American Society of Echocardiography.14 Left ventricular (LV) mass was calculated from LV linear dimensions and indexed to height2.7 and body surface area (BSA). LV volumes were derived according to the modified biplane Simpson's method in the apical four-chamber and/or two-chamber views and indexed to height2.7 and BSA. Relative wall thickness (RWT) was calculated by the formula: (2×diastolic posterior wall thickness)/end diastolic LV diameter. We studied sex differences in LV geometry patterns. LV hypertrophy (LVH) was defined as LVM indexed to height2.7 >44 g/m2.7 in women and >48 g/m2.7 in men. Normal geometry was classified as LVM/left ventricular end diastolic volume (LVEDV) ratio ≤1.5 and no LVH. Concentric remodeling (CR) was defined as LVM/LVEDV >1.5 and no LVH. Concentric hypertrophy (CH) was defined as LVM/LVEDV >1.5 and LVH. Eccentric hypertrophy (EH) was defined as LVM/LVEDV ≤1.5 and LVH.15

Diastolic parameters

Mitral flow velocities were assessed by positioning the sample volume of pulsed wave Doppler at the tip of the mitral leaflets from the apical four-chamber view. Tissue Doppler E' velocity was measured as the average of the values detected at the septal and lateral mitral annulus. Left atrial volume was assessed by the biplane area-length method from apical two-chamber and four-chamber views at end systole from the frame preceding mitral valve opening, and indexed to BSA and to height2.7. Pulmonary artery systolic pressure (PASP) was estimated using Doppler tricuspid regurgitant velocity (V) as PASP= 4 (V2) + 10 mm Hg.

Systolic parameters

LVEF was calculated from LV end-diastolic volume and LV end-systolic volume. Tissue Doppler Imaging (TDI) mitral S' velocity was measured as the average of the values detected at the septal and lateral mitral annulus. Using a vendor-independent 2D speckle tracking software (2D Cardiac Performance Analysis version 4.5, TomTec Imaging Systems, Munich, Germany), we assessed longitudinal and radial strain in 215 participants, and circumferential deformation in 143 subjects. Deformation imaging data were obtained using apical four chamber and two chamber views for longitudinal and radial systolic strain, and the mid LV short axis view for circumferential systolic strain. For strain analysis we excluded patients with non DICOM images, lack of a full cardiac cycle, more than 1 segment dropout or significant foreshortening of the left ventricle.

Noninvasive estimation of ventricular-vascular stiffness

LV diastolic stiffness was characterized as LV diastolic elastance (Ed), calculated as the ratio of E/E' (index of mean left atrial pressure) to LV end diastolic volume, and as Ed indexed to BSA. LV systolic stiffness was characterized as end-systolic elastance (Ees), which was calculated using the modified single-beat method from stroke volume (SV), arm-cuff pressures, and pre-ejection and total systolic periods determined on pulsed-wave Doppler of aortic flow, LVEF, and an estimated normalized ventricular elastance at arterial end diastole, as previously validated against invasive assessment.16 We also detected LV end systolic stiffness indexed to BSA.

Arterial stiffness was characterized as effective arterial elastance (Ea),17 and as the individual components of arterial load, systemic arterial compliance (SAC)18 and systemic vascular resistance index (SVRi). Ea was estimated as end-systolic pressure (ESP) divided by SV, determined echocardiographically using the Simpson's method of discs; LV ESP was calculated as 0.9 multiplied by arm cuff systolic blood pressure (SBP) detected at the time of echocardiography. SAC was estimated as the ratio between SV and pulse pressure. SVRi was estimated by the formula: (mean arterial pressure/cardiac index) * 80. Vascular/ventricular coupling was assessed as the ratio Ea/Ees. To

account for differences in body size, we indexed all LV volumes to BSA or height2.7, and used the indexed LV volumes for calculation of indexed Ea.

Statistical Analysis

Subjects in PARAMOUNT were stratified according to sex with continuous data presented as mean and standard deviation or median and interquartile range. Categorical variables are shown as counts and percentages. Log transformation was applied to skewed variables (NTproBNP, urine albumin to creatinine ratio (UACR)). Clinical characteristics and cardiac structure and function were compared between men and women using 2-sided Student t tests with unequal variance, X2 test or Fisher exact tests, as determined by variable type and distributional shape. Multivariable adjusted linear and logistic regression models were used to assess the association between echocardiographic parameters of cardiac structure and function (outcome variables) and sex after adjusting for significant covariates known to be related to the outcome of interest and that differed by sex at univariable screen: age, diabetes, SBP at the time of echocardiogram, heart rate, NYHA class, history of myocardial infarction, BMI, and presence of albuminuria, defined as UACR ≥17 mg/g in men and ≥25 mg/g in women.19 For deformation analysis, the model was further adjusted for baseline LVEF. For analyses of Ees or Ed, the model was further adjusted for LV geometry (LV mass/LV end diastolic volume), recognizing that this parameter is an important determinant of LV chamber elastance properties.20-2122

Predictors of eccentric versus concentric LV geometry, including baseline characteristics, were assessed via multivariate logistic regression models using a stepwise forward selection procedure, with p-value threshold of 0.15.

All tests were two-sided and P-values of<0.05 were considered statistically significant. Statistical analyses were performed with the STATA software package (version 12, Stata Corp, College Station, Texas).

Table 1: Baseline characteristics of the study population by sex

	Men (n=120)	Women (n=159)	P-value
Age (year)	70±10	71 ± 9	0.11
NYHA II	103 (86)	120 (75)	0.048
NYHA III	16 (13)	38 (24)	
Fatigue	58 (48)	92 (59)	0.08
Rales	7 (6)	9 (6)	1.00
Edema	37 (31)	51 (32)	0.83
Previous Hospitalization for HF	58 (48)	62 (39)	0.12
Date of HF diagnosis			
Less than 1 year	48 (40)	60 (38)	0.70
More than 1 year	72 (60)	99 (62)	
Atrial Fibrillation at screening	38 (32)	43 (27)	0.40
Hypertension	109 (91)	151 (95)	0.18
Diabetes	53 (44)	54 (34)	0.08
Glycated hemoglobin (%)	6.5±1.2	6.4±1.0	0.40
Myocardial Infarction	40 (33)	18 (11)	<0.001
Current Smoker	11 (9)	6 (4)	0.08
Heart Rate (beats per min)	69±13	70±13	0.44
Systolic Blood Pressure (mm Hg)	134±16	137±15	0.13
Diastolic Blood Pressure (mm Hg)	77±10	78±10	0.60
Pulse Pressure (mm Hg)	57±14	59±15	0.21
Mean Arterial pressure (mmHg)	101±10	102±10	0.22
Body Mass Index (kg/m^2)	29.4±5.1	30.7 ±6.2	0.049
Obesity	47 (39)	82 (42)	0.040
eGFR (mL/min/1.73 m^2)	67±20	64±21	0.30
CKD	47 (39)	68 (43)	0.55
UACR (mg/g)	19 [8,64]	12 [6,32]	0.055
Albuminuria	57 (54)	39 (29)	<0.001
Hemoglobin (g/dl)	13.9±1.8	13.2±1.5	0.001
Anemia	34 (30)	31 (20)	0.059
NT-proBNP (pg/mL)	947 [494,1490]	828 [507,1287]	0.31

Data are counts (%), mean ± SD, median [IQR].
NYHA= New York Heart Association; HF= heart failure; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; UACR= urine albumin to creatinine ratio. Obesity defined as BMI≥ 30 kg/ m2 ; CKD defined as eGFR<60 ml/min/1.73 m2; albuminuria defined as UACR≥17 mg/g in men and ≥25 mg/g in females; anemia defined as Hb <12 g/dl in females and < 13 g/dl in males.

Results

Clinical characteristics

Of the 279 patients included in this analysis 159 (57%) were women. Table 1 shows baseline characteristics of the study population stratified by sex. Age did not differ between the groups, whereas women were more obese. The rate of previous admission for HF and the duration of the disease did not vary by sex, while CAD was less common in females. Despite similar medical therapy and NTproBNP values,

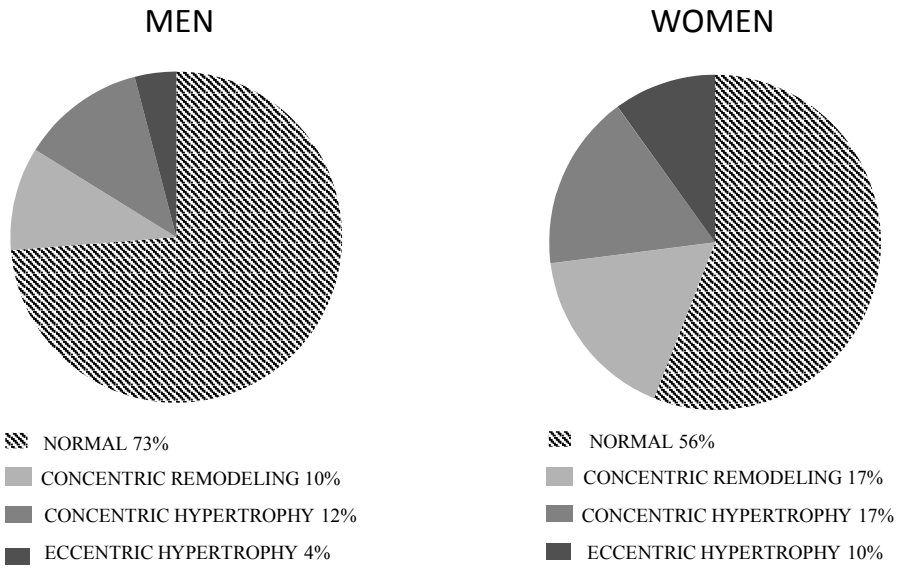

Figure 1: Prevalence of LV geometry patterns by sex. CR= concentric remodeling; CH=concentric hypertrophy; EH=eccentric hypertrophy. Unadjusted p value 0.028, adjusted p value 0.056 (adjusted for age, diabetes, SBP, heart rate, NYHA class, history of myocardial infarction, BMI, and presence of albuminuria)

women were more symptomatic, having less II NYHA class and more III class. There was a trend toward less diabetes and anemia (using sex specific cut off values for hemoglobin: <12 g/dl for women and < 13 g/dl for men) in women compared to men. Women were less likely to have albuminuria, while chronic kidney disease (CKD), defined as eGFR< 60 ml/min per 1.73 m2, did not vary between the groups.

Sex differences in cardiac structure

After adjustment for age, diabetes, SBP, and significant covariates that differed by sex in univariable analyses, women had higher indexed LV wall thicknesses, while LV mass and LV volumes indexed for height2.7 were similar. RWT and LVM/LVEDV ratio were not significantly different between sexes (Table 2). Plotting the sex differences in LV geometry (we considered normal geometry versus CR, or CH, or EH) there was a trend towards more abnormal LV geometry in women compared to men (unadjusted p=0.028, adjusted p=0.056, Figure 1).

Multivariate logistic regression showed that the only clinical correlate of eccentric hypertrophy (considering all the variables included in Table 1) was a higher NYHA functional class (OR 4.4, 95% CI 1.4-13.8; p 0.010). Conversely, a concentric phenotype (remodeling or hypertrophy) was significantly associated only with female sex (OR 2.6, 95% CI 1.3-5.0; p 0.006).

Sex differences in LV diastolic function

LV diastolic function was more impaired in women than men, as reflected by more impaired LV relaxation (lower E'), higher LV filling pressure (higher E/E'), and greater LV diastolic stiffness (higher Ed) (Table 2 and 3). Additionally, Ed indexed to BSA was significantly higher in women compared to men (0.29±0.15 vs 0.19±0.09), both in unadjusted ($p<0.001$) and adjusted analysis ($p<0.001$).

Sex differences in LV systolic function

Despite higher LVEF in women, overall pump function, as assessed by stroke volume index and deformation imaging parameters, was similar between men and women, while S' mitral velocity was lower in women. In contrast, LV systolic stiffness (Ees) was higher in women than men, even after adjusting for LV geometry (LV mass/LV end diastolic volume), or indexing for BSA (women 4.94±1.86, men 4.28±1.70, unadjusted p=0.006, adjusted p=0.046).

Sex differences in arterial stiffness

Women had higher arterial stiffness (Ea) compared to men, although the difference was not significant after adjusting for height2.7. The higher absolute values of Ea in women were matched to higher Ees, such that there was no sex difference in the vascular-LV coupling ratio. Since Ea is an index of arterial load reflective of both pulsatile and resistive load and influenced by heart rate, we further studied the separate components of pulsatile (systemic arterial compliance, SAC) and resistive (systemic vascular resistance index, SVRi) load. SAC was lower in women than men, even after adjusting for clinical covariates and heart rate. In contrast, SVRi was similar in women and men. Sex differences in arterial elastance were therefore principally reflective of differences in oscillatory properties.

Table 2: Cardiovascular structure and function of the study population by sex

	Males (n=120)	Females (n=159)	P (unadjusted)	P (adjusted)[a]
SWT (cm)	0.97±0.19	0.94±0.17	0.28	0.28
SWT indexed to $hgt^{2.7}$ ($cm/m^{2.7}$)	0.23±0.05	0.28±0.06	<0.001	<0.001
SWT indexed to BSA (cm/m^2)	0.49±0.11	0.53±0.11	0.005	0.002
PWT (cm)	0.88±0.17	0.85±0.15	0.10	0.07
PWT indexed to $hgt^{2.7}$ ($cm/m^{2.7}$)	0.21±0.05	0.25±0.05	<0.001	<0.001
PWT indexed to BSA (cm/m^2)	0.45±0.10	0.48±0.10	0.010	0.005
LVM (g)	162±47	136±34	<0.001	<0.001
LVM indexed to $hgt^{2.7}$ ($g/m^{2.7}$)	38.5±12.0	39.5±10.7	0.47	0.39
LVM indexed to BSA (g/m^2)	82.6±24.6	76.5±19.9	0.023	0.26
LVEDV (ml)	130±32	102±22	<0.001	<0.001
LVEDV indexed to $hgt^{2.7}$ ($ml/m^{2.7}$)	30.7±8.0	29.6±7.1	0.23	0.73
LVEDV indexed to BSA (ml/m^2)	66.2±16.7	57.2±12.6	<0.001	0.005
LVESV (ml)	59±22	41±13	<0.001	<0.001
LVESV indexed to $hgt^{2.7}$ ($ml/m^{2.7}$)	14.0±5.5	11.9±3.9	<0.001	0.10
LVESV indexed to BSA (mL/m^2)	30.1±11.7	23±7.3	<0.001	0.001
RWT (cm)	0.368±0.082	0.384±0.083	0.10	0.48
LVM/LVEDV (g/ml)	1.30±0.43	1.38±0.40	0.16	0.34
SV (ml)	71±17	61±14	<0.001	<0.001
SV indexed to $hgt^{2.7}$ ($ml/m^{2.7}$)	16.7±3.9	17.7±4.4	0.060	0.20
SV indexed to BSA (ml/m^2)	36.1±8.5	34.2±7.9	0.054	0.22
LA volume (ml)	69±28	64±24	0.10	0.023
LA volume indexed to $hgt^{2.7}$ ($ml/m^{2.7}$)	16.2±6.5	18.7±7.3	0.004	0.08
LA volume indexed to BSA (ml/m^2)	35.1±13.9	36.3±13.3	0.45	0.77
LVEF (%)	55.5±8	60.1±6.9	<0.001	0.012
S' (cm/s)	6.6±1.6	6.2±1.4	0.06	0.037
Global Longitudinal Strain (%)	-14.5±3.2	-14.8±3.4	0.53	0.28[b]
Global Circumferential Strain (%)	-22.4±6.2	-23.4±5.8	0.33	0.24[b]
Global Radial Strain (%)	21.1±6.9	22.6±9.7	0.21	0.50[b]
E (cm/s)	76.8±27.4	87.4±29.2	0.002	0.001
A (cm/s)	71.6±20.9	79.2±29.5	0.06	0.017
E/A	1.2±0.7	1.0±0.5	0.18	0.10
E' (cm/s)	7.1±2.3	6.3±2.1	0.009	0.002
E/E'	12.1±4.8	15.8±7.1	<0.001	<0.001
PASP (mmHg)	35±8	37±9	0.47	0.16
MR jet area/LA area	5.4±2.7	6.0±3.1	0.21	0.18

Data are mean ± SD.
Hgt= height. BSA= body surface area. LVEDD= left ventricular end diastolic diameter. LVESD= left ventricular end systolic diameter. SWT= septal wall thickness. PWT= posterior wall thickness. RWT=relative wall thickness. LVM= left ventricular mass. LVEDV= left ventricular end diastolic volume. LVESV= left ventricular end systolic volume. SV= stroke volume. LA= left atrial. LVEF=left ventricular ejection fraction. S'= TDI systolic mitral annulus velocity. E= early mitral inflow velocity. A= late mitral inflow velocity. E/A=early to late mitral inflow velocity ratio. E'= mitral relaxation velocity. E/E'=mitral inflow to mitral relaxation velocity ratio. PASP=pulmonary artery systolic pressure. MR= mitral regurgitation.
a adjusted for age, diabetes, NYHA class, history of myocardial infarction, BMI, systolic blood pressure, presence of albuminuria, heart rate.
b adjusted for age, diabetes, NYHA class, history of myocardial infarction, BMI, systolic blood pressure, presence of albuminuria, heart rate, and EF

Discussion

Our study highlights sex differences in clinical characteristics and vascular-LV structure and function among patients with HFpEF. Women with HFpEF were less likely affected by CAD and more obese than men with HFpEF. Compared to men, women also displayed more impaired

LV diastolic function (lower E', higher E/E'), LV diastolic stiffening (higher Ed), and LV systolic stiffening (higher Ees), associated with a trend towards more abnormal LV geometry. There were no sex differences in systolic arterial-LV coupling. These findings contribute to our understanding of the predisposition of women to HFpEF.

The clinical differences between women and men described in PARAMOUNT parallel those seen previously in other HFpEF studies,1,11,23 and mimic the characteristics that distinguish HFpEF from HFrEF in the community.2,24 These findings could contribute to the predominance of women compared to men carrying the burden of HFpEF compared to HFrEF. Since aging, hypertension, and obesity may have a different impact on cardiac structure and function, arterial elastance, and endothelial dysfunction in women and men,3,5,8,25-262728 they represent a possible explanation for sex disparities in cardiovascular remodelling in HFpEF.

Women have been shown to display a steeper increase of LV mass with aging.4 Furthermore, so-called normal aging has been demonstrated to worsen LV diastolic function more in women than in men.7,8,29 In the PARAMOUNT study, women displayed greater cardiac functional abnormalities compared to men with HFpEF. Additionally, our current findings of possible sex differences in LV geometry are consistent with previous data from the community, where women had a greater degree of LVH in response to hypertension and obesity compared to men.6 Furthermore, it is noteworthy that the extent of LVH was not very marked in our population. This is consistent with epidemiologic data in HFpEF 30 and underscore that the presence of LVH is not a prerequisite for the development of HFpEF. Nonetheless, it is also possible that in a sicker population more extensive LV remodeling might have been found, and some sex differences potentiated.

Of note, the encountered sex based differences in cardiac structure and function in our HFpEF population are consistent with "intrinsic" sex differences in LV structure and function in the absence of HF.7,8,28,31,32 Sex differences appear to be greater in the presence of risk factors for HFpEF, and further exaggerated when HFpEF develops. Importantly, our data show that these differences persisted after adjustment for comorbidities and age, suggesting

that the enhanced LV diastolic dysfunction and systolic stiffening in women with HFpEF may be secondary to sex-specific mechanisms. Indeed, sex hormones have been suggested as a possible explanation for the female predisposition to develop LV diastolic dysfunction and HFpEF.33-343536 In particular, reduced levels of estrogens in post-menopausal women have been linked to activation of the renin–angiotensin system, alterations in renal sodium handling, and inhibition of nitric oxide and natriuretic peptides.31,33

Recent studies have also shown that myocardial cGMP production may be more dependent on natriuretic peptide signaling in men and on nitric oxide signaling in women.37,38 Thus, loss of estrogen signaling in menopause may predispose women to reductions in myocardial cGMP, greater LV diastolic dysfunction and development of HFPEF.39 At the same time, the duration of estrogen exposure, modifications at the estrogen receptor level, as well as levels of androgens seem to contribute to sex differences in cardiovascular structure and function.32,33 These sex based time varying phenomena matches with the recently observed changes of diastolic function,30 LV systolic function, and functional reserve across the lifespan in both sexes, which become more impaired in women compared to men in the postmenopausal years, despite similar or enhanced function in women during youth.40 Furthermore, hormone levels are believed to partly justify sex based disparities in arterial properties, with higher arterial stiffening described in aged women than men.8,41,42 However, multiple factors affecting the arterial tree differ between the two sexes, including discrepancies in body height, heart rate, and smaller arterial diameters in women.43 Since women have on average smaller body size and arterial length than men, they have an earlier wave reflection, which tends to amplify the pressure wave in systole rather than diastole, and may account for lower vascular compliance in women.44 Concordantly, in our study we found a higher arterial elastance (Ea) in women compared to men, which may have been related to sex based differences in height or BSA, as demonstrated by Ea indexed measures (Eai). Nonetheless other studies using applanation tonometry have shown that the sex differences in arterial wave reflection are not fully accounted for by

Table 3: Vascular and ventricular stiffness parameters by sex

	Males (n=120)	Females (n=159)	P (unadjusted)	P (adjusted)[a]
Ed	0.10±0.05	0.17±0.08	<0.001	<0.001 [b]
Ea (mm Hg/ml)	1.8±0.5	2.1±0.5	<0.001	<0.001
Ea indexed to $hgt^{2.7}$ (mm Hg·$m^{2.7}$/ml)	7.6±1.9	7.4±2.0	0.31	0.27
Ea indexed to BSA (mm Hg·m^2/ml)	3.5±0.9	3.8±1.0	0.028	0.26
SAC (ml/mm Hg)	1.31±0.43	1.10±0.37	<0.001	<0.001
SVRi (dyn·s·cm^{-5}·m^2)	3377±956	3555±1060	0.15	0.19
Ees (mm Hg/ml)	2.1±0.8	2.7±1.0	<0.001	<0.001 [b]
Ea/Ees	0.92±0.35	0.88±0.51	0.49	0.48

Data are mean ± SD.
BSA= body surface area. Ed= left ventricular diastolic stiffness. Ea= effective arterial elastance. SAC= systemic arterial compliance. SVRi= systemic vascular resistance index. Ees= left ventricular end systolic elastance. Ea/Ees= ventricular/vascular coupling.
a adjusted for age, diabetes, NYHA class, history of myocardial infarction, BMI, systolic blood pressure, presence of albuminuria, heart rate.
b adjusted for age, diabetes, NYHA class, history of myocardial infarction, BMI, systolic blood pressure, presence of albuminuria, heart rate, and LV mass/LV end diastolic volume.

morphometric differences, and may also be due to differences in the physical properties of the vascular tree (i.e. arterial stiffness).45 Thus the higher absolute Ea in women than men, although not significant after adjusting for height, may still be of clinical importance.

Finally we observed a higher mean LVEF in women compared to men with HFpEF, consistent with previous reports11,12,24 and with the known 5% difference in LVEF described as a “normal LVEF gap” expected between the sexes.46 Since SVi was not significantly different by sex, the higher LVEF in women was primarily due to the smaller LV end diastolic volume index denominator in women. This is consistent with findings reported in the MESA population.47 In our study, LVEF was higher in women with HFpEF despite lower mitral S’ velocities and similar systolic longitudinal strain, compared to men with HFpEF. Sex differences in tissue Doppler velocities, but not in global longitudinal strain, were consistent in systole and diastole and suggest that the two modalities may provide different information. Indeed, global longitudinal strain has been shown to be less load-dependent than tissue Doppler velocities.48 Overall, these results indicate that the higher LVEF in women may be related to differences in LV structure rather than a true increase in myocardial contractility.

Limitations of this analysis should be noted. First, the cross-

sectional nature of the data precludes conclusions about causality. Second, we did not assess diastolic indices or ventricular/arterial mechanical properties using invasive measures. Although invasive methods are considered the gold standard, repeated invasive studies to characterize ventricular/arterial mechanics would not have been feasible in this large sample. Furthermore all echoes were analyzed in an experienced echo-core laboratory. Third, our results may not be generalizable to HFpEF population in the community, given the inclusion and exclusion criteria of the PARAMOUNT trial. The PARAMOUNT study population was a stable, compensated chronic HFpEF population with only mildly elevated LV filling pressures and PASP at rest despite a validated diagnosis of HF in every case. Nonetheless, baseline characteristics of our patients were largely similar to those described in previous HFpEF epidemiological studies .11,49-5051

In conclusion, there are prominent sex differences in clinical characteristics and vascular-LV structure and function among patients with HFpEF. Our data show that more pronounced diastolic dysfunction may contribute to the greater predisposition to HFpEF in women compared with men.

Funding: Novartis Pharmaceuticals, East Hanover, NJ
Conflict of interest: MZ, BP, AAV, JJM, MP, AMS, SDS have received research support and have consulted for Novartis. TB and ML are employees of Novartis. MG, CSL, DKG, ABSS, SC, BC, EKK declare that they have no conflict of interest.

REFERENCES

1 Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:18-28.

2 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.

3 Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? Curr Opin Cardiol 2011;26:562-8.

4 Lieb W, Xanthakis V, Sullivan LM, Aragam J, Pencina MJ, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham offspring study. Circulation 2009;119:3085-92.

5 Cheng S, Xanthakis V, Sullivan LM, Lieb W, Massaro J, Aragam J, Benjamin EJ, Vasan RS. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: longitudinal observations from the Framingham Heart Study. Circulation 2010;122:570-8.

6 Kuch B, Muscholl M, Luchner A, Döring A, Riegger GA, Schunkert H, Hense HW. Gender specific differences in left ventricular adaptation to obesity and hypertension. J Hum Hypertens 1998;12:685-91.

7 Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging 2010;3:614-22.

8 Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation 2005;112:2254-62.

9 Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol 2013;61:96-103.

10 Shim CY, Park S, Choi D, Yang WI, Cho IJ, Choi EY, Chung N, Ha JW. Sex differences in central hemodynamics and their relationship to left ventricular diastolic function. J Am Coll Cardiol 2011;57:1226-33.

11 Kitzman DW, Gardin JM, Gottdiener JS, Arnold A, Boineau R, Aurigemma G, Marino EK, Lyles M, Cushman M, Enright PL; Cardiovascular Health Study Research Group. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001;87:413-9.

12 Galvao M, Kalman J, DeMarco T, Fonarow GC, Galvin C, Ghali JK, Moskowitz RM. Gender differences in in-hospital management and

outcomes in patients with decompensated heart failure: analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Card Fail 2006;12:100-7.

13 Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387-95.

14 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.

15 Gaasch WH, Zile MR. Left Ventricular Structural Remodeling in Health and Disease. With Special Emphasis on Volume, Mass, and Geometry. J Am Coll Cardiol 2011;58:1733–40

16 Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028-34.

17 Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513-21.

18 Chemla D, Hébert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274:H500-5.

19 Levey AS, Cattran D, Friedman A, Miller WG, Sedor J, Tuttle K, Kasiske B, Hostetter T. Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis 2009;54:205-26.

20 Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501-12.

21 Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left

ventricular chamber function. Cardiovasc Res 2001;49:340-50.
22 Chantler PD, Lakatta EG, Njjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol 2008;105:1342-51.
23 Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, McKelvie RS, McMurray JJ, Zile MR, Massie BM, Kitzman DW. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2012;5:571-8.
24 Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750-7.
25 McManus DD, Xanthakis V, Sullivan LM, Zachariah J, Aragam J, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left atrial diameter over the adult life course: Clinical correlates in the community. Circulation 2010;121:667-74.
26 Piro M, Della Bona R, Abbate A, Biasucci LM, Crea F. Sex-related differences in myocardial remodeling. J Am Coll Cardiol 2010;55:1057-65.
27 De Simone G, Devereux RB, Chinali M, Roman MJ, Barac A, Panza JA, Lee ET, Howard BV. Sex differences in obesity-related changes in left ventricular morphology: the Strong Heart Study. J Hypertens 2011;29:1431-8.
28 Hamburg NM, Palmisano J, Larson MG, Sullivan LM, Lehman BT, Vasan RS, Levy D, Mitchell GF, Vita JA, Benjamin EJ. Relation of brachial and digital measures of vascular function in the community: the Framingham heart study. Hypertension 2011;57:390-6.
29 Okura H, Takada Y, Yamabe A, Kubo T, Asawa K, Ozaki T, Yamagishi H, Toda I, Yoshiyama M, Yoshikawa J, Yoshida K. Age- and gender-specific changes in the left ventricular relaxation: a Doppler echocardiographic study in healthy individuals. Circ Cardiovasc Imaging 2009;2:41-6.
30 Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115(15):1982-90.
31 Borlaug BA, Redfield MM, Melenovsky V, Kane GC, Karon BL, Jacobsen SJ, Rodeheffer RJ. Longitudinal changes in left ventricular stiffness: a community-based study. Circ Heart Fail 2013;6(5):944-52.
32 Salton CJ, Chuang ML, O'Donnell CJ, Kupka MJ, Larson MG, Kissinger KV, Edelman RR, Levy D, Manning WJ. Gender differences and normal

left ventricular anatomy in an adult population free of hypertension. A cardiovascular magnetic resonance study of the Framingham Heart Study Offspring cohort. J Am Coll Cardiol 2002;39(6):1055-60.
33 Fischer M, Baessler A, Schunkert H. Renin angiotensin system and gender differences in the cardiovascular system. Cardiovasc Res 2002;53:672-7.
34 Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. Nat Rev Drug Discov 2006;5:425-38.
35 Lam CS, Little WC. Sex and cardiovascular risk: are women advantaged or men disadvantaged? Circulation 2012;126:913-5.
36 Lam CS, Cheng S, Choong K, Larson MG, Murabito JM, Newton-Cheh C, Bhasin S, McCabe EL, Miller KK, Redfield MM, Vasan RS, Coviello AD, Wang TJ. Influence of sex and hormone status on circulating natriuretic peptides. J Am Coll Cardiol 2011;58:618-26.
37 Wong PG, Armstrong DW, Tse MY, Brander EP, Pang SC. Sex-specific differences in natriuretic peptide and nitric oxide synthase expression in ANP gene-disrupted mice. Mol Cell Biochem 2013;374(1-2):125-35.
38 Wong PG, Armstrong DW, Tse MY, Ventura NM, Pang SC.Contribution of Estrogen to Sex Dimorphic Expression of Cardiac Natriuretic Peptide and Nitric Oxide Synthase Systems in ANP Gene-Disrupted Mice. Open Journal of Endocrine and Metabolic Diseases 2013, 3: 1-11
39 Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodeling Through Coronary Microvascular Endothelial Inflammation. J Am Coll Cardiol. 2013;62 (4):263-71.
40 Föll D, Jung B, Schilli E, Staehle F, Geibel A, Hennig J, Bode C, Markl M. Magnetic resonance tissue phase mapping of myocardial motion: new insight in age and gender. Circ Cardiovasc Imaging 2010;3:54-64.
41 Thompson J, Khalil RA. Gender differences in the regulation of vascular tone. Clin Exp Pharmacol Physiol 2003;30:1-15.
42 Rajkumar C, Kingwell BA, Cameron JD, Waddell T, Mehra R, Christophidis N,Komesaroff PA, McGrath B, Jennings GL, Sudhir K, Dart AM. Hormonal therapy increases arterial compliance in postmenopausal women. J Am Coll Cardiol 1997;30:350-6.
43 Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM. Influence of body height on pulsatile arterial hemodynamic data. J Am Coll Cardiol. 1998;31:1103-9.
44 London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure. Role of body height. Hypertension 1995;26:514-9.
45 Lieber A, Millasseau S, Bourhis L, Blacher J, Protogerou A, Levy BI, Safar ME. Aortic wave reflection in women and men. Am J Physiol Heart Circ

Physiol 2010;299:H236-42.
46 Chung AK, Das SR, Leonard D, Peshock RM, Kazi F, Abdullah SM, Canham RM, Levine BD, Drazner MH. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume: the Dallas Heart Study. Circulation 2006;113:1597-604.
47 Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging 2009;2:191-8.
48 Carluccio E, Biagioli P, Alunni G, Murrone A, Leonelli V, Pantano P, Biscottini E, Paulus WJ, Ambrosio G. Advantages of deformation indices over systolic velocities in assessment of longitudinal systolic function in patients with heart failure and normal ejection fraction. Eur J Heart Fail 2011;13(3):292-302.
49 Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948-55.
50 Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209-16.
51 Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002;137:631-9.

Chapter 5

Clinical implications for patients with heart failure with preserved ejection fraction

5.1. Heart failure with preserved ejection fraction: a clinical dilemma.

Komajda M, Lam CS. Eur Heart J. 2014 Apr;35(16):1022-32

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ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) is now recognized as a major and growing public health problem worldwide. Yet significant uncertainties still surround its pathophysiology and treatment, leaving clinicians in a dilemma regarding its optimal management. Whether HFpEF and Heart Failure with Reduced Ejection Fraction (HFrEF) are two distinct entities or two ends of a common spectrum remains a matter of debate. In particular, the lack of benefit observed with renin angiotensin system blockers has raised questions regarding our understanding of the pathophysiology of HFpEF. New paradigms including a prominent role of comorbidities, inflammation, endothelial dysfunction and pro-hypertrophic signalling pathways have been proposed. Recent proof of concept trials using a phosphodiesterase inhibitor, a mineralocorticoid receptor antagonist, an angiotensin receptor / neprilysin inhibitor, a soluble guanylate cyclase stimulator or a sino atrial If current blocker provide important insight for the development of novel therapeutic strategies in HFpEF.

INTRODUCTION

Historically, clinical trials in heart failure (HF) required a low left ventricular ejection fraction (LVEF), a rather crude measurement of cardiac function, as an inclusion criterion. Indeed, these clinical trials in HF with reduced EF (HFrEF) were highly successful in identifying effective therapies which improved survival in HFrEF. However, large epidemiologic studies subsequently demonstrated that HF could occur in the presence of a normal LVEF, and in fact, patients with so-called HF with preserved ejection fraction (HFpEF) may represent up to half of the HF population. In contrast to HFrEF, outcomes in HFpEF have not improved over the last decades, underscoring our continued lack of effective therapies for this important syndrome.2,3

The purpose of this review is to provide a global perspective on HFpEF, to discuss the controversies surrounding the disease syndrome, to analyse the reasons for failure of clinical trials to improve outcomes, and to gain insight from recent proof of concept trials.

IS HFpEF A SPECIFIC SYNDROME?

Does the syndrome of HFpEF exist?

The concept that HFpEF existed as an entity was challenged until two decades ago, as reflected in the statement from the 1995 European Society of Cardiology (ESC) Guidelines for the diagnosis of HF4 that "Conclusive evidence that most elderly patients with a diagnostic label of HF but with normal systolic function at rest do indeed have HF is lacking." ESC current guidelines now fully acknowledge HFpEF as an important HF syndrome, in line with robust evidence that (i) HFpEF comprises almost half the HF population in epidemiologic studies;5 (ii) classic hemodynamic changes of HF are present in HFpEF (elevated left ventricular filling pressures and abnormal vasorelaxation in both the systemic and pulmonary circulations);6-9 and (iii) neurohormonal activation characteristic of HF (renin-angiotensin-aldosterone axis, sympathetic nervous system) also occurs in HFpEF.10-11

Is HFpEF just a transitory stage in the HF spectrum or is it a distinct disease phenotype?

The dilemma of whether to consider HFpEF as part of the same disease process as "conventional" HFrEF, as opposed to a distinct

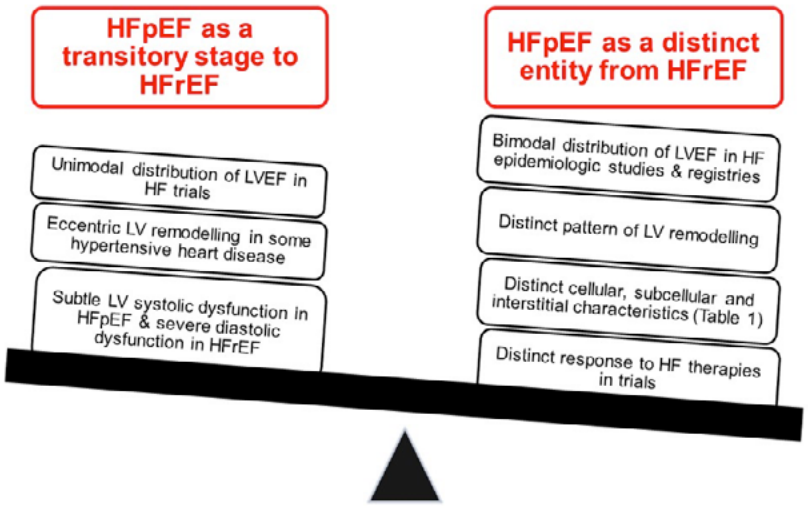


Figure 1: Arguments for HFpEF as a transitory stage to HFrEF (left) versus HFpEF as a distinct entity from HFrEF (right)
LV: left ventricular, EF: ejection fraction

disease entity in itself, remains unresolved (Figure 1).12-13 The demonstration of a unimodal distribution of LVEF in patients with HF from the CHARM Programme14 and the IMPROVEMENT of Heart Failure Programme;15 the existence of subtle left ventricular systolic dysfunction in HFpEF and of diastolic dysfunction in HFrEF;16-19 as well as the progression to eccentric left ventricular remodelling and HFrEF in hypertensive heart disease20;all argue for HFpEF and HFrEF being overlapping syndromes or stages in the same disease process. However, a bimodal distribution of LVEF was revealed after accounting for the larger proportion of patients with low ejection fraction enrolled in the CHARM Programme21 and after stratification by sex in prior registries.22 Two independent studies of patients with chronic HF with a wide range of ejection fraction; the OPTIMIZE Registry of patients with acute HF23, as well as the community-based study from Olmsted County,13 have also confirmed the bimodal distribution of ejection fraction among large numbers of patients with HF, thus providing strong argument for two separate diseases. In addition, the evolution of preserved to reduced ejection fraction in hypertensive heart disease has been shown to be a rare occurrence, and to be largely attributable to an interim myocardial infarction in these uncommon cases.24-25

Finally, despite overlapping systolic and diastolic abnormalities, there are fundamental differences in the pattern of left ventricular remodelling at the chamber and ultra-structural levels, and the response to therapeutic interventions, between HFpEF and HFrEF. Left ventricular chamber dilation (eccentric remodelling) is a specific characteristic of HFrEF, whereas in HFpEF chamber size is normal or near normal with increased wall thickness relative to chamber dimension (concentric remodelling).6,10,26-30 These distinct structural changes in HFrEF versus HFpEF are also associated with distinct functional consequences involving in particular the left ventricular end-systolic pressure-volume relationship.18,26,31,32 The slope of the end-systolic pressure-volume relationship, or end-systolic elastance, is markedly reduced in HFrEF but elevated in HFpEF (Figure 2A). As a result, patients with HFrEF respond favorably to arterial vasodilators, with minimal drop in blood pressure and substantial improvement in stroke volume.32 In contrast, the steeper end-systolic pressure-volume relationship in HFpEF implies a marked sensitivity to volume changes

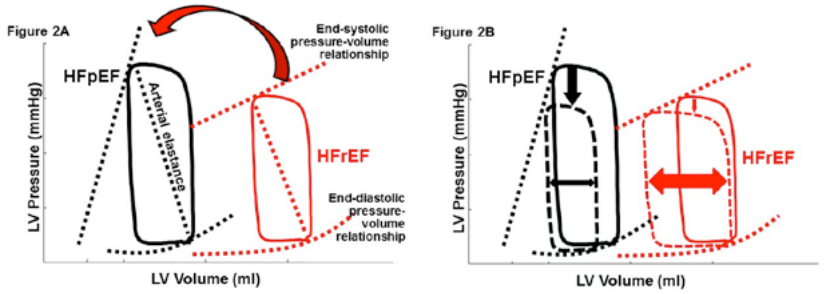
Table 1. Cellular, subcellular and interstitial differences between HFpEF and HFrEF

	HFpEF	HFrEF
Cardiomyocyte diameter	↑	↓
Myofibrillar density	↑	↓
Passive cardiomyocyte resting tension	↑↑	↑
Cardiomyocyte calcium sensitivity	↑↑	↑
Abnormal phosphorylation of sarcomeric proteins	↑↑	↑
Titin isoform N2BA/N2B ratio	↓	↑
Myocardial protein kinase G activity	↓	↑
Myocardial oxidative stress	↑	↔
Myocardial cyclic guanosine monophosphate concentration	↓	↑
Myocardial pro-B-type natriuretic peptide-108 expression	↔/↑	↑↑
Mysial collagen volume fraction	↑	↓
Perivascular collagen volume fraction	↑	↑↑
Scar-related collagen volume fraction	↑	↑↑
Endomyocardial MMP-1:TIMP-1 ratio	↔	↑↑
Myocardial advanced glycation end products in diabetic HF	↑	↑↑

References: 30, 36 - 41

and more exaggerated drops in blood pressure with vasodilator therapy (Figure 2B). These differences in ventricular-vascular function may partially explain the failure of vasodilators to improve outcomes in clinical trials for HFpEF33-35 unlike what was observed in HFrEF.

Differences between HFpEF and HFrEF extend to the tissue and to the cellular level (Table 1): cardiomyocytes are narrow and elongated in HFrEF, with reduced myofibrillar density, whereas myocyte diameter and resting tension are both increased in HFpEF. At the subcellular level, there is an increased ratio of the stiffer isoform of the macromolecule titin in HFpEF compared with HFrEF, which may contribute to higher resting tension and the larger drop in tension in response to phosphorylation. Finally, at the level of the interstitium, matrix collagen turnover differs between HFrEF and HFpEF, where changes in matrix metalloproteinases and their inhibitors favouring



Figures 2A and 2B: Pressure volume loop characteristics in HFpEF (black) and HFrEF (red) in baseline conditions (2A), and in response to vasodilators (2B)
2A: Curved arrow depicts the steeper end-systolic pressure-volume relationship in HFpEF compared to HFrEF. **2B:** Pressure-volume loops before (solid) and after (dotted) administration of vasodilators. Arrows contrast the drop in blood pressure and changes in stroke volume between HFpEF and HFrEF in response to vasodilators. In HFrEF, administration of arterial vasodilators results in minimal drop in blood pressure and substantial improvement in stroke volume. In contrast, the steeper end-systolic pressure-volume relationship in HFpEF results in more exaggerated drops in blood pressure with vasodilator therapy, with potential reduction in stroke volume.

increased extracellular matrix degradation appear to predominate in HFrEF.30,36-41

Does HFpEF simply represent a collection of comorbidities rather than a pathophysiologically distinct entity?

Since HFpEF is a disease of the elderly, it is not surprising that age-related comorbidities are highly prevalent among HFpEF patients, including cardiovascular (e.g. atrial fibrillation) and non-cardiovascular (e.g. renal impairment, chronic lung diseases, anemia, obesity, cancer, liver disease, peptic ulcer disease, and hypothyroidism) comorbidities.5 Indeed, the Charlson index, a weighted prognostic score of comorbidity, was ≥3 in 70% of community-based HFpEF patients27 indicating a high comorbidity burden. Comorbidities herald the onset of symptomatic decompensation in HFpEF, contribute to ventricular-vascular dysfunction, influence functional status and impact prognosis.42-45

The recognition of the importance of comorbidities in HFpEF has led some to question if HFpEF simply represents a collection of comorbidities in elderly breathless patients, rather than a distinct disease entity.46 However, a comparison of mortality in patients from HFpEF

trials to patients with similar age, gender and comorbidity distribution in other cardiovascular trials of hypertension, coronary heart disease, and diabetes mellitus shows striking differences47 : a much higher mortality was observed in HFpEF trials despite a lower comorbidity burden compared to non-HFpEF trial patients. Similarly, cardiovascular parameters were compared among HFpEF patients, age-/gender-matched healthy controls and hypertensive patients without HF from the Olmsted County.43 Adjusting for covariates, comorbidities (obesity, anemia, diabetes and renal dysfunction) impacted ventricular-vascular profile and survival, but could not fully account for the more severe cardiovascular abnormalities in HFpEF compared to healthy controls and hypertensive controls without HF. Thus, the worse prognosis and more severe cardiovascular dysfunction in HFpEF compared to patients with cardiovascular risk factors but without HF, suggest that HFpEF is not merely about old age and comorbidities but that it is an independent entity.

Is HFpEF a uniform syndrome?

The term “diastolic HF” was first coined to reflect the leading pathophysiologic factor believed to cause the syndrome – left ventricular diastolic dysfunction. In a landmark study,6 abnormalities in left ventricular relaxation and compliance were uniformly demonstrated in 47 cases of HF despite a normal ejection fraction. However, population-based studies also showed that left ventricular diastolic dysfunction

Table 2: Heterogeneity of HFpEF

Pathophysiologic mechanisms	Clinical phenotypes
LV diastolic dysfunction	“Pure” diastolic heart failure
Systolic LV-arterial stiffening Abnormal LV-arterial coupling	“Common” HFpEF (associated with hypertension, obesity, diabetes)
Myocardial contractile dysfunction	Coronary artery disease- associated
Impaired exercise reserve Chronotropic incompetence	Early HFpEF (with exercise-induced diastolic dysfunction)
Left atrial dysfunction	Atrial fibrillation- predominant
Pulmonary hypertension	Pulmonary hypertension and/or right heart failure
Volume overload Endothelial dysfunction	Non-cardiac cause – related volume overload (such as chronic kidney disease or anemia)

was present in a large proportion of community-based adults without HF,48 and that patients with “systolic HF” were even more likely to have moderate/severe diastolic dysfunction compared to patients with so-called “diastolic HF”27 Nonetheless, progression of left ventricular diastolic dysfunction was found to be a major mechanism distinguishing HFpEF from age-, sex- and body size-matched healthy controls and hypertensive individuals without HF in the general community.26

Other mechanistic studies challenged the concept that HFpEF was a uniform syndrome of “diastolic HF”. These studies described various abnormalities beyond diastolic dysfunction, including abnormal ventricular-arterial coupling with exercise,28,31 impaired systemic vasodilator reserve,7,28 chronotropic incompetence,7,49 myocardial contractile dysfunction despite a normal ejection fraction,18,50 left atrial dysfunction,51 pulmonary hypertension with intrinsic pulmonary vascular disease,9,52 endothelial dysfunction,28,53 and volume overload (related to extra-cardiac causes such as obesity, chronic kidney disease, or anemia).54 It is possible that each of these mechanistic studies selected a specific subset of patients with HFpEF: only 2% of hospitalized patients with HFpEF were eligible in a study of static and dynamic left ventricular diastolic function.55 This, in turn, suggests that HFpEF is not a single homogeneous syndrome, but is rather a heterogeneous condition consisting of several pathophysiological sub-types.56 It has in particular been proposed that three subtypes of HFpEF patients exist: those with exercise induced diastolic dysfunction, those with chronic volume overload and those with associated right HF and/or pulmonary hypertension. The phenotype heterogeneity of HFpEF is probably more complex as illustrated in Table 2. The use of novel analytic strategies such as “phenomapping” where dense multidimensional data are used to distinguish different phenotypes might be helpful in this respect.

The importance of recognizing the heterogeneity of the pathophysiology in HFpEF is highlighted by the fact that a “one size fits all” approach for clinical trials in HFpEF has been disappointing and that treatments directed at HFpEF as a large undifferentiated group have failed to improve outcomes. Understanding the heterogeneity of HFpEF and improved phenotypic characterization of mechanistic sub-

types might therefore allow the design of more targeted HFpEF clinical trials.

HOW IS THE DIAGNOSIS OF HFpEF ESTABLISHED?

The accurate diagnosis of HFpEF remains a challenging and controversial topic. Several diagnostic criteria have been proposed.58-61 The original criteria58 were criticized for a lack of sensitivity, since the definitive diagnosis mandated determination of ejection fraction within 72h of presentation and invasive demonstration of left ventricular diastolic dysfunction -a situation which is rarely performed or even available to clinicians. The stipulation that ejection fraction had to be measured during periods of acute decompensation was deemed unnecessary in later guidelines, since these acute measurements were shown to be similar to those performed after in-hospital stabilization.62

The need for invasive demonstration of left ventricular diastolic abnormalities was also questioned, since these were shown to be uniformly present in patients with clinical HF and a normal ejection fraction, suggesting that the diagnosis could rely on the presence of clinical HF and a normal ejection fraction alone.6

However, given the lack of specificity of symptoms of HF, as well as the co-existence of age-related comorbidities that could explain the symptoms, some form of demonstration of left ventricular diastolic dysfunction is deemed necessary : the ESC consensus provided practical recommendations on the evaluation of diastolic dysfunction using echocardiography (both Doppler-based as well as structural assessments of LV mass and left atrial size), measurement of natriuretic peptides, and the presence of atrial fibrillation, in addition to cardiac catheterization.60 The most recent version of the ESC Heart Failure guidelines further expanded these criteria and includes “relevant structural heart disease (left ventricular hypertrophy/ left atrial enlargement)” in addition to, or as an alternative to, the demonstration of diastolic dysfunction.1

In general, all proposed diagnostic criteria to date share three features in common (Figure 3): (1) clinical signs or symptoms of HF; (2) evidence of preserved ejection fraction; and (3) evidence of abnormal left ventricular structure and/or diastolic dysfunction. Some

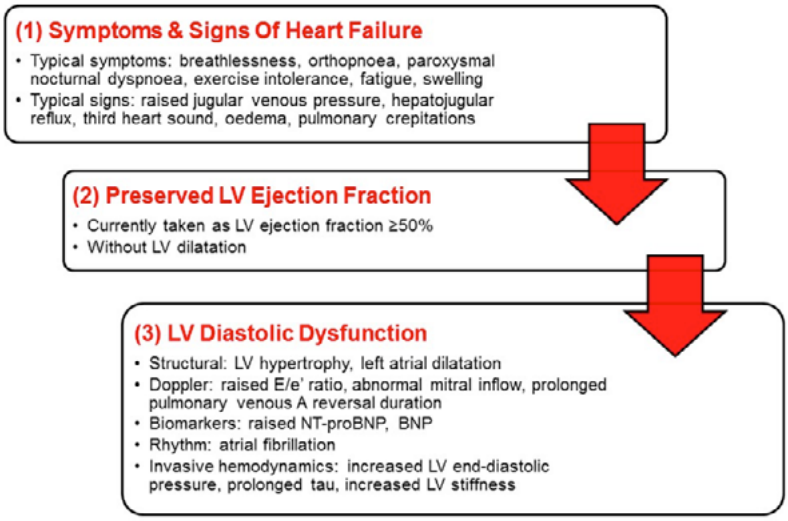


Figure 3: Scheme for diagnosis of HFpEF. In general, all proposed diagnostic criteria to date share three features in common: (1) symptoms and signs of heart failure; (2) evidence of preserved left ventricular (LV) ejection fraction; and (3) evidence of LV diastolic dysfunction, which may include structural, Doppler echocardiographic, biomarker, rhythm or invasive hemodynamic criteria.

issues are not fully addressed in the available guidelines: (1) the lack of sensitivity in patients who have increased filling pressures only during exercise (but not at rest); (2) the phenotypic diversity of HFpEF and the identification of pathophysiologically distinct subsets; (3) the impact and significance of important comorbidities on diagnostic thresholds. Other areas of continued controversy include the optimal cut-off to define “preserved” or “normal” ejection fraction, and how to classify patients who are in the “gray zone” (40-50%) or those who transition between ejection fraction zones.63 Furthermore, none of the published criteria have been prospectively tested for their diagnostic utility in large cohorts of unselected patients.

HOW DO PATIENTS WITH HFpEF DIE?

Since multiple age-related comorbidities may co-exist in patients with HFpEF, knowledge of cause-specific mortality, and not just all-cause mortality alone, is important to discern the risk related to the comorbidity versus the risk associated with HFpEF itself.

Numerous studies have now shown that the mortality burden

of HFpEF is substantial, ranging from 10-30% annually, and is higher in epidemiologic studies than clinical trials.64 The pooled death rate in HFpEF was 121 (95% confidence interval [CI]: 117, 126) deaths per 1000 patient-years in a meta-analysis of 31 studies.65 Mortality rates are clearly elevated compared to age- and comorbidity-matched controls without HF,48 and may be as high as in HFrEF.2,3 The majority of deaths in HFpEF are cardiovascular deaths, 51-60% of deaths in epidemiologic studies,66 and ~70% in clinical trials. Among cardiovascular deaths, sudden death and HF death are the leading cardiac modes of death in HFpEF clinical trials.67,68 However, compared to HFrEF, the proportions of cardiovascular deaths, sudden death and HF deaths are lower in HFpEF and conversely, non-cardiovascular deaths constitute a higher proportion of deaths in HFpEF than HFrEF, particularly in epidemiologic studies.65

A greater non-cardiac comorbidity burden in HFpEF offers a potentially simple explanation for the mortality differences between epidemiologic studies and clinical trials, or between HFpEF and HFrEF. However, the extent to which non-cardiac comorbidities predict death in HFPEF remains unclear, and non-cardiac comorbidities alone do not explain mortality differences between different HF cohorts. For example, in the Olmsted County studies, the burden of non-cardiac comorbidities was similar between HFpEF and HFrEF groups, yet the proportion of non-cardiovascular deaths was higher in the former.3 The extent of coronary artery disease appears to be inversely related to non-cardiovascular deaths in both the Olmsted County community-based cohort and in the clinical trial population from TIME-CHF69: a lower baseline proportion of coronary artery disease was related to a higher proportion of non-cardiovascular deaths in HFpEF versus HFrEF. A potential explanation for these observations is that patients with HFpEF “escape” death related to coronary artery disease and subsequently die from their non-cardiac comorbidities. Alternatively, patients with coronary artery disease may have been more likely to “transition” to HFrEF following a myocardial infarction, thus enriching the HFrEF population eventually with more coronary heart deaths.

HOW ARE PATIENTS WITH HFpEF TREATED?

Current international guidelines acknowledge a lack of evidence in the management of HFpEF. The ESC recommends the use of diuretic agents to relieve breathlessness and oedema, an optimal management of hypertension or myocardial ischaemia, and to control heart rate since elevated heart rate is usually poorly tolerated in these patients with stiff left ventricle.1

The pattern of HF medications prescriptions differs significantly between HFpEF and HFrEF. In the large OPTIMIZE HF registry, a lower rate of prescription of ACE inhibitors, aldosterone antagonists, betablockers, loop diuretics, digoxin and a higher rate of use of amlodipine were observed in patients with HFpEF than in those with HFrEF both at admission and discharge. This trend also existed comparing patients with EF > 50% and those with 40% £ EF £ 50%.23 The international meta-analysis MAGGIC using individual data from randomized clinical trials, from observational studies and from management strategy controlled trials found a similar pattern of prescription results in 10.347 HFpEF patients compared to 31.625 HFrEF patients.65

Betablockers and calcium channel blockers.

Slowing the heart rate should result in an increase in the diastolic filling period in an abnormally stiff left ventricle with prolonged relaxation. However, slowing the heart rate in the absence of increased heart rate tends to prolong diastasis where transmitral flow plays a minor role.70 In addition, there is a high prevalence of chronotropic incompetence in HFpEF which is associated to exercise limitation, and chronotropic reserve might be a key factor to increase cardiac output during exercise.28,71

In this context, the role of betablockers remains uncertain. Nebivolol, a third generation betablocker, was tested in 2.128 patients > 70 years with a history of HF or known ejection fraction < 35% in the SENIOR trial.72 There was a 14% reduction in the primary composite outcome (all cause mortality or cardiovascular admission). A similar benefit was observed in those patients with an EF > 35% (approximately 1/3 of the total number)73 or <35%. Since the threshold of EF used

Table 3 : Outcome trials in HFpEF

	PEP CHF	CHARM PRESERVED	I-PRESERVE	TOP CAT
Reference	35	33	34	100
N patients	850	3.023	4.128	3.445
Drug tested	Perindopril	Candesartan	Irbesartan	Spironolactone
Target dose (mg/day)	4	32	300	30/45
Mean follow-up (months)	26.2	36.6	49.5	42 estimate
Age at inclusion (years)	≥ 70	≥ 18	≥ 60	≥ 50
Mean age (years)	76	67	72	68.6
Men / Women %	45 / 55	60 / 40	40 / 60	48 / 52
HF aetiology				
Ischaemic	26*	57	25	59
Hypertensive	79*	23	64	91**
EF% at inclusion	LV WMI* 1.4 – 1.6	> 40	≥ 45	≥ 45
BNP/NT proBNP at inclusion (pg/ml)	-	-	-	> 360 (NT proBNp) > 100 (BNP)
NT proBNP/BNP Median value at baseline (pg/ml)	453(Pbo)/335(Active)	-	320(Pbo)/360(Active)	950(NT proBNP)/234(BNP)
BMI (kg/m²)	27.5	29	30	32
6 minute walk test (m)	297(Pbo)/290(Perindopril)	N/A	N/A	N/A
Primary composite endpoint	All cause mortality / HF hospitalization	CV death / HF hospitalization	All cause death / CV hospitalization	CV death / HF hospitalization / aborted cardiac arrest
Hazard ratio	0.92 (0.70-1.21)	0.89 (0.77-1.03)	0.95 (0.86-1.05)	N/A
P Value	0.54	0.12	0.35	-

* Prior hypertension / prior myocardial infarction for PEP CHF ; ** Hypertension history TOP CAT

was very low (35%), no definite conclusion can be drawn from this subgroup of patients about the applicability of results to patient with HFpEF where EF≥50%. In addition, an echocardiographic substudy did not show any effect of Nebivolol on parameters of systolic or diastolic dysfunction.74

In another study, ELANDD, Nebivolol did not influence symptoms or exercise capacity in HFpEF; however there was a direct correlation between the decrease of peak heart rate and the decrease of peak oxygen consumption in the Nebivolol group.75 In the OPTIMIZE HF registry, a risk and propensity adjusted model was used which showed no significant relationship between discharge use of betablockers and mortality and/or rehospitalisation rate at 60 to 90 days.23 Finally, in the COHERE registry (Carvedilol Heart Failure Registry), the benefit of Carvedilol on mortality, clinical status and need for hospitalisations76 was lower in patients with EF > 40%. Conversely, prescription of betablockers was associated with a marked mortality reduction in a cohort of HFpEF patients followed-up for 25 months.77

Data regarding the heart rate lowering calcium channel blocker Verapamil are scarce. A small size study suggested some improvement of symptoms and of exercise capacity in these patients.78

There is therefore no conclusive evidence for the benefit (or lack of benefit) of beta-blockers or verapamil in HFpEF.

ACE-inhibitors and angiotensin receptor blockers.

Three outcome trials have been conducted in HFpEF with ACE inhibitors or angiotensin receptor blockers (Table 3). The rationale in the use of a renin angiotensin system antagonist (RAS) is to block the pro-hypertrophic and pro-fibrotic effects of Angiotensin-II.

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM Preserved) trial included 3.023 patients with an ejection fraction > 40%.33 In the active arm, Candesartan was uptitrated to 32 mg/day. This trial failed to demonstrate a significant benefit on cardiovascular mortality whereas a reduction in HF hospitalisations was observed.

The Perindopril for Elderly People with Chronic Heart Failure trial (PEP CHF) enrolled elderly patients with EF > 40% and with

echocardiographic evidence of diastolic dysfunction.35 No reduction in the occurrence of the primary composite endpoint (all cause mortality or HF hospitalisation) was observed in the Perindopril arm titrated to 4 mg/day. A long recruitment period with, as a result, a number of crossovers together with the limited sample size (n = 850) might explain the neutral result of this trial. A post hoc analysis performed after one year of follow-up, suggested indeed a favourable trend in the Perindopril arm.

The large Irbesartan in HF with Preserved Systolic Function trial (I-PRESERVE) enrolled 4.128 elderly HF patients with EF > 45% who were randomly assigned to Irbesartan or placebo.34 No reduction in the composite outcome (all cause mortality or cardiovascular hospitalisation) or in any secondary outcome was observed after nearly 50 months of follow-up.

These disappointing results with ACE-inhibitors / ARBs contrast with the benefit observed in HFrEF. However, in a large prospective cohort of unselected HFpEF patients form Sweden, the use of a renin

Table 4: Recent proof of concept studies

	Aldo DHF	**PARAMOUNT**	**RELAX**
Reference	99	96	93
N patients	422	266	216
Drug	Spironolactone	Angiotensin Receptor Neprylisin inhibitor (LCZ 696) vs Valsartan	Sildenafil
Men / Women (%)	48/52	43/57	52/48
Mean age (years)	67	71	69
Baseline E/E'	12.7	12.4 / 13	16
6mn walk test (m)	-	N/A	305(Pbo)/308 (Sildenafil)
Target dose (mg/ day)	25	400 (ARNi)/320 (Valsartan)	60 -12 weeks 180 -12 weeks
EF at inclusion (%)	≥ 50	≥ 45	≥ 50
NT proBNP at inclusion (pg/ml)	-	≥ 400	≥ 400 <400 if elevated LV filling pressure
NT proBNP baseline geometric mean (pg/ml)	-	794(ARNi)/870 (Valsartan)	-
Median (pg/ml)	148(Pbo)/179 (Spironolactone)	828(ARNi)/939 (Valsartan)	648(Pbo)/757 (Sildenafil)
Primary endpoint	E/E' /peak VO^2	Change NT proBNP	Change Peak VO^2
Duration	12 months	12 weeks	24 weeks

angiotensin system antagonist was associated with a lower all cause mortality.79

Digoxin

In the Digitalis Interaction Group trial (DIG), a subgroup of 988 patients with EF > 45% was randomized to placebo or to Digoxin. No difference was observed in all cause, HF or cardiovascular mortality, or in the composite outcomes of HF death or hospitalisation, or all cause mortality or cause specific mortality after 37 months of follow-up.80 However, a trend towards a reduction of HF hospitalization was observed together with a trend for increased hospitalization for unstable angina.

WHY DID THE PRIOR TRIALS FAIL?

A. Patient factorsp

The identification of patients with HFpEF is particularly challenging since: (i) signs and symptoms of HF are not specific and may be observed in other conditions such as obesity, anemia, renal dysfunction or pulmonary disease -- all conditions which are frequently associated with HFpEF ; (ii) there is no real consensus on the definition of “normal” ejection fraction: The ESC guidelines recommend a threshold of 50% but randomized clinical trials conducted in HFpEF have used lower values (>40% CHARM Preserved, >45% I-PRESERVE) which might indicate an already significantly altered systolic performance and, hence a clinical profile closer to that observed in HFrEF ; (iii) invasive confirmation of the presence of left ventricular diastolic dysfunction is not feasible in daily practice and non-invasive markers are therefore needed: A central place has been given to the Echo-Doppler E/E’ ratio but there is increasing use of surrogate markers including left atrial enlargement, left ventricular hypertrophy or raised natriuretic peptide plasma levels. The only randomized clinical trial using comprehensive echo parameters of diastolic dysfunction was PEP CHF.35 The concern therefore remains that the patients recruited in the neutral trials above did not have HFpEF but had left ventricular hypertrophy with a non-cardiac reason for dyspnea such as obesity. Nonetheless, the fact remains that the rate of cardiovascular mortality or HF hospitalizations is much higher in HFpEF trials than that observed in clinical trials on

hypertension with or without left ventricular hypertrophy, suggesting that patients enrolled in these HFpEF trials indeed had HF.47

B. Disease factors

An analysis of the inclusion criteria of the outcome trials as well as that of recent proof of concept studies including Aldo-DHF, PARAMOUNT or RELAX reveals notable heterogeneity with regards to age or level of neurohormonal stimulation as assessed by BNP/NT proBNP plasma level (Table 4). This suggests differences in the stage of disease of patients enrolled in these trials. Elderly HFpEF patients with a long standing history of hypertension and significant accumulation of cardiac extracellular matrix may be poor responders to any pharmacological intervention ("too sick to benefit")

For instance, a post-hoc analysis of I-PRESERVE showed that Irbesartan improved clinical outcomes in those patients with below the median values of NT proBNP but not in those with higher levels.81 It is therefore possible that a pharmacological intervention using an ARB would benefit at an earlier stage of the disease.

On the other hand, it was argued that spironolactone was not ideally tested in Aldo-DHF since patients were "too well" and had only mild cardiac dysfunction based on E/E' value, NT proBNP plasma levels and exercise capacity. This explanation was put forward to explain the lack of improvement of exercise capacity in patients with early stage HFpEF.82 Yet, in the Exercise Training in Diastolic Heart Failure–Pilot (Ex-DHF-Pilot) Study, exercise training was effective at increasing peak VO2 in patients with similarly early stage HFpEF83. Furthermore, half of the patients in Aldo-DHF had disease that was advanced enough to fulfil ESC criteria of HFpEF, and the effects of spironolactone on E/e' and peak VO2 in these patients were similar in those who did not fulfil the ESC criteria. It would therefore appear that pharmacological and non-pharmacological therapeutic approaches in HFpEF vary in their effects on exercise capacity at different stages of the disease.

C. Trial factors

The outcome trials PEP CHF and I-PRESERVE were associated with a prolonged recruitment period. This is likely attributable to the inherent difficulties in confirming the clinical diagnosis of HFpEF and the need for cardiac imaging expertise. As a result of the trial prolongation, a high rate of drop-out was observed together with a significant number of randomized patients receiving an open label RAS antagonist during the course of the trials. In I-PRESERVE, approximately 1/5 of patients randomized to Irbesartan were prescribed an ACE inhibitor during the follow-up period and 1/3 dropped out of the active arm. Similarly in PEP CHF, 40% of the patients randomized to Perindopril and 36% of those randomized to placebo stopped the study treatment and 1/3 received an open label ACE inhibitor.

As discussed above, cardiovascular mortality and morbidity are the most prevalent outcomes in HFpEF.67,68 However, the proportion of patients dying of non cardiovascular causes increases with ejection fraction.14 Cardiovascular drugs such as RAS antagonists might therefore have a limited effect in a condition where the non cardiovascular mode of death is more prevalent and sudden cardiac death or HF death less prevalent than in HFrEF.

D. Drug factors

Both ACE inhibitors and ARBs are associated with a significant reduction in morbidity and mortality in HFrEF.

The final pathway of these two classes is to inhibit the synthesis or the action of Angiotensin II and Aldosterone which promote cardiac fibrosis and hypertrophy. In addition, ARBs have been shown to be more efficient on left ventricular hypertrophy than beta-blockers in hypertension.84 There is therefore no clear explanation why blockade of the RAS system failed to bring benefit in HFpEF. In particular it is unknown whether the different pattern of remodelling may explain this finding.

A lower level of neurohormonal stimulation assessed by NT proBNP / BNP has been reported in HFpEF than in HFrEF and up to 1/3 of patients show plasma levels within the normal range.85 However, in HFpEF, NT proBNP elevation remains a very powerful predictor of poor outcome.86

Also, increased plasma levels of peripheral collagen turnover markers were not influenced by Irbesartan in I-PRESERVE although fibrosis and increased extracellular matrix are believed to be key factors in HFpEF.87

It is therefore possible that a differential pattern of neurohormonal activation and its downstream consequences plays a role in the lack of response reported so far in HFpEF with RAS antagonists.

Overall, the lack of benefit of traditional HF therapies in HFpEF underscores our lack of understanding of the pathophysiology of this syndrome, emphasizes that a uniform “blanket rule” approach does not work in HFpEF, and supports the view that HFpEF is indeed a distinct syndrome from HFrEF. A paradigm shift in our understanding of the mechanisms that may be targeted in HFpEF, and the patients most likely to benefit from these targeted approaches, is urgently needed.

NEW PARADIGM IN HFpEF

A new paradigm based on observation of specific myocardial structural and functional changes observed in HFpEF has been put forward88. This paradigm emphasizes the role of a pro-inflammatory state with widespread endothelial dysfunction, leading to reduced nitric oxide (NO) bioavailability in cardiomyocytes, reduced myocardial cyclic guanosine 3’, 5’-monophosphate (cGMP) content and low protein kinase-G activity (PKG).

The central role of the NO-cGMP-PKG pathway is described in this paradigm (Figure 4): Endothelial dysfunction has been shown to be highly prevalent and independently predictive of survival in HFpEF, suggesting that it plays a major role in the pathophysiology of HFpEF89-90. Endothelial dysfunction occurs in diabetes and hypertension, both important risk factors for HFpEF, and causes oxidative stress with high levels of reactive oxygen species which interfere with NO production in endothelial cells. This leads to reduced NO bioavailability to adjacent cells such as cardiomyocytes. cGMP is the second messenger that plays a role in various key physiologic pathways, including cardiovascular homeostasis, cellular growth and contractility, and inflammation. Guanylate cyclases are enzymes that catalyze the conversion of guanosine-5’-triphosphate to cGMP.

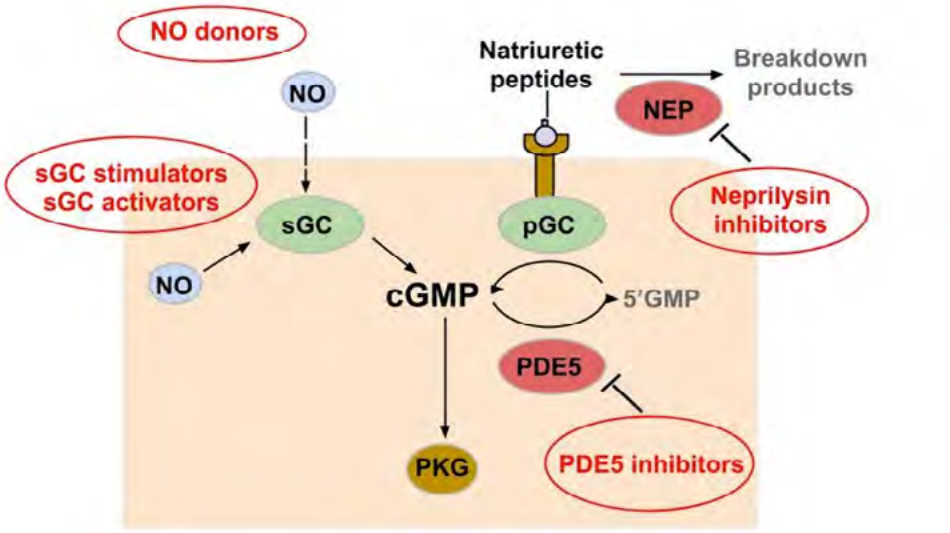


Figure 4: Role of nitric oxide (NO) - cyclic guanosine 3', 5'-monophosphate (cGMP) - protein kinase-G activity (PKG) pathway in HFpEF. NO: nitric oxide ; sGC: soluble guanylate cyclase ; NEP: neutral endopeptidase ; pGC: particular guanylate cyclase ; PKG: protein kinase G ; PDE5: phosphodiesterase-5 ; cGMP: cyclic guanylate monophosphate

Membrane-bound particulate guanylate cyclase (pGC) serves as a receptor for natriuretic peptides, whereas soluble guanylate cyclase (sGC) acts as a receptor for NO. Subsequently, cGMP effectors include cGMP-dependent protein kinases, such as PKG. The disruption of the NO–cGMP-PKG signalling pathway can therefore explain the development of concentric LV remodelling, increased stiffness of the cardiomyocyte through hypo-phosphorylation of titin, and increased collagen deposition in HFpEF (Figure 4).

LESSONS FROM RECENT PROOF OF CONCEPT STUDIES.

(Table 4)

Until now, attempts to target the NO-cGMP-PKG pathway in HFpEF have been unsuccessful. Administration of exogenous nitrates or NO donors is dependent on biotransformation to the active, nitric oxide-containing compound and is limited by tolerance in the long term or can even paradoxically cause endothelial dysfunction, oxidative stress, and release of endothelin-1.91

1°) Phosphodiesterase-5 inhibitors

Since cGMP is inactivated by Phosphodiesterase-5 (PDE-5), blockade of cGMP degradation by inhibition of PDE-5 could have beneficial effects such as improvement in cardiac relaxation and left ventricular reverse remodelling.

Experimental data suggest that PDE-5 over-expression induces cardiac cardiomyocyte hypertrophy and that this is reversed by the selective PDE-5 inhibitor Sildenafil.92

A small clinical study showed that Sildenafil improved left ventricular diastolic function, hypertrophy and reduced pulmonary pressures after twelve months of exposure in HFpEF patients with pulmonary hypertension.93

However, these beneficial effects were not confirmed by the RELAX trial including 216 elderly HFpEF patients.94 After 24 weeks of treatment, no effect on maximal exercise capacity, on six minutes walk distance, on clinical status, quality of life, left ventricular remodelling or diastolic function was observed.

Several explanations have been put forward in order to explain these neutral results: absence of pulmonary hypertension, high prevalence of chronotropic incompetence, insufficient duration of the trial. Basal plasma levels of NT proBNP were also markedly elevated, suggesting that these patients were in an advanced stage of the disease and, therefore, less likely to benefit from this pharmacological intervention. Furthermore, it is postulated that impaired cGMP production, rather than increased degradation, may be the predominant pathophysiologic mechanism in HFpEF. This may explain the relative lack of effectiveness of therapies targeting inhibition of cGMP degradation, and suggest that stimulation of cGMP production may be an important therapeutic strategy in HFpEF.

2) Soluble guanylate cyclase stimulators

Small molecules can directly stimulate the sGC pathway with a dual mode of action: the sensitization of sGC to endogenous NO by stabilizing the NO-sGC binding and direct stimulation of sGC via an NO independent binding site.

The Phase IIa Acute hemoDynamic effects of rIociguat in

patients with puLmonary hypertension Associated with diasTolic heart failurE (DILATE-1) study characterized the hemodynamic effects, safety, and pharmacokinetics of three different single doses of riociguat, a sGC stimulator, in patients with HFpEF and pulmonary hypertension.95 There was no significant change in the primary endpoint of peak change in mPAP from baseline to 6 hours in the riociguat 2 mg arm vs placebo. Riociguat significantly increased stroke volume and decreased systolic blood pressure without significantly changing pulmonary vascular resistance, transpulmonary pressure gradient, or heart rate. Importantly, riociguat was well tolerated, and increased flow did not result in increased left ventricular filling pressures.

These results will need to be compared to the Soluble Guanylate Cyclase stimulator Heart Failure Studies (SOCRATES)-Preserved trial is a placebo-controlled double-blind dose-finding phase IIb study in which a new oral sGC stimulator BAY1021189 will be tested in patients with worsening chronic HFpEF requiring hospitalization (clinicaltrials.gov identifier NCT01951638

3°) Neprilysin inhibitors

LCZ 696 is a complex molecule (angiotensin receptor Neprilysin inhibitor) which combines an inhibitory effect of Neprilysin (endopeptidase 24-11) together with an angiotensin receptor blocker. Neprilysin is the enzyme responsible for the degradation of biologically active natriuretic peptides. The blockade of Neprilysin increases intracellular cGMP and improves relaxation and hypertrophy.96 This new compound was tested against Valsartan in 301 HFpEF patients treated for 36 weeks in the PARAMOUNT trial.97

The primary endpoint was the change in NT proBNP, a marker of wall stress, from baseline to 12 weeks. LCZ 696 significantly reduced the plasma level of NT proBNP compared to Valsartan but the difference was no longer significant at 36 weeks. Left atrial volume and dimension were also favourably influenced at the end of the trial whereas there was no change in other echocardiographic parameters, including diastolic function.

These encouraging results deserve confirmation and a large outcome study is planned to determine if this new class might be

beneficial in HFpEF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction [PARAGON-HF], ClinicalTrials.gov Identifier: NCT01920711).

4°) Mineralocorticoid Receptor Antagonists.

Activation of the mineralocorticoid receptor by Aldosterone results in sodium retention, cardiac fibrosis, endothelial dysfunction and cardiac hypertrophy.98 Small studies suggest that mineralocorticoid receptor antagonists (MRAs) might be beneficial in diastolic HF.99 In the Aldosterone receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial, 422 HFpEF patients were randomized to Spironolactone 25 mg/day or placebo and followed-up for 12 months.100

Diastolic function assessed primarily by the e/e' ratio on Doppler-Echocardiography was significantly but modestly improved by Spironolactone, along with reduction in left ventricular mass and NT-proBNP; whereas no change was observed in maximal exercise capacity, patient symptoms or quality of life.

An explanation put forward to explain the lack of change in exercise capacity was the fact that patients enrolled in this trial had only mild cardiac dysfunction and modest symptom limitation at baseline. Of note, even in HFrEF where mineralocorticoid receptor antagonists are considered a Class I therapy, spironolactone had only a marginal effect on functional capacity in HFrEF patients101 despite significant effects on left ventricular remodelling.

It therefore remains possible that mineralocorticoid antagonism in HFpEF may, in spite of limited impact on symptoms, lead to outcome benefits in mortality and morbidity. The large outcome trial TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) has just been completed. It compares Spironolactone uptitrated to 45 mg/day vs placebo on a composite outcome of cardiovascular mortality, aborted cardiac arrest or HF hospitalization in an elderly population of 3.445 patients.100 The results are expected shortly.

5°) Ranolazine

Ranolazine is a selective inhibitor of the late sodium (INa+)current which is activated in HF and leads to Ca2+ overload, impaired relaxation and pro-arrhythmic after depolarizations.102

The RALI DHF trial was a small trial including 20 patients which suggested that Ranolazine administered intravenously for 24 hours modestly improved hemodynamic parameters but had no effect on relaxation.103

The acute phase was followed by 13 days of oral administration which did not result in any change of echocardiographic parameters, NT proBNP or exercise performance.

The ERIPE study (EUDRA CT n° 2011-000805-27) is currently evaluating the effect of Ranolazine on six minutes walking distance and on Echo-Doppler parameters in 120 patients treated for 26 weeks.

6°) Ivabradine

Ivabradine is an inhibitor of the sino atrial node If current and reduces elevated heart rates. It has shown benefit in HFrEF in sinus rhythm and with elevated heart rate.104 Selective heart rate reduction improves diastolic filling by prolonging the diastole without significant lusitropic or inotropic effects.105

In a mouse model of diabetes with diastolic dysfunction, Ivabradine reduced effective arterial elastance, increased aortic distensibility and decreased left ventricular end-systolic elastance106. In addition, a favourable effect was observed on the activity of SERCA 2a, a key player in the uptake of calcium by the sarcoplasmic reticulum. Recently, 61 patients with HFpEF and an increased baseline heart rate were assigned to Ivabradine 5mg bid or placebo for seven days.107 A significant increase was observed in exercise capacity with a contribution from left ventricular improved filling pressure response to exercise as reflected by e/e' ratio. These results are short term and need confirmation. The EDIFY study (EUDRA CT n° 2012 002742-20) will enroll 400 HFpEF patients and will assess the effect of Ivabradine uptitrated to 10 mg bid on e/e' ratio as well as on other echocardiographic parameters, on six minutes walking distance and on NT proBNP plasma levels after 8 months of follow-up.

7°) Advanced glycation end products cross link breakers.

Increased diastolic left ventricular stiffness is a marker of left ventricular dysfunction induced by diabetes mellitus, a major comorbidity in HFpEF. This has been related to myocardial deposition of advanced glycation end products (AGEs) which are formed by oxidative or non-oxidative reactions between proteins and carbohydrates and form cross links in the extracellular matrix.108

AGEs cross link breakers such as alagebrium chloride have been tested in experimental models and in a small open label clinical study enrolling 23 elderly patients with diastolic HF.109 After 16 weeks of follow-up, an improvement in diastolic function was observed. Whether this class might have beneficial effects in patients with HFpEF and diabetes needs to be evaluated in a properly designed large-scale and longer-term clinical trial.

8°) Other potential perspectives

Statins

By blocking the activity of several Guanosine Triphosphate binding proteins, statins suppress left ventricular hypertrophy and decrease collagen synthesis in experimental models.110,111. However, in the clinical area, only one small study suggested a beneficial effect of statins on mortality in HFpEF patients112 whereas in the GISSI HF trial, no benefit was observed with Rosuvastatin in the 10% of patients enrolled with relatively preserved ejection fraction.113

Calcium cycling modulators

Ryanodine receptors which trigger calcium release from the intracellular stores, the sarcoplasmic reticulum, are dysfunctional in HF and lead to Ca2+ leakage, impaired relaxation and after depolarizations.114 A Ryanodine receptor stabilizer, K 201, has been tested in vitro with favourable effects115 but there are as yet no data on the clinical effects of this compound. Down regulation of the sarcoplasmic reticulum Ca2+ ATPase 2a isoform (SERCA2), which is responsible for the reuptake of calcium in the sarcoplasmic reticulum, is observed in HF and leads to impaired relaxation. A non-pharmacological approach using SERCA2 gene treatments by an adenovirus has been tested with some promising results in HFrEF.116 Whether this approach could be beneficial in HFpEF deserves consideration.

Micro RNAs

In the last 5 years, evidence has rapidly accumulated indicating a pivotal role for micro RNAs (miRNAs), a class of small non-coding RNAs, in cardiovascular development and response to injury.117,118 Precursor “primary” miRNAs undergo processing to the mature form which binds with complementary sequences on target messenger RNA and prevents translation and /or accelerates degradation of message RNA. MicroRNAs may also return to the nucleus and act upon DNA as transcription factors. MiRNAs have been shown to be differentially expressed in the failing myocardium and to play an important role in progression of HF by targeting genes that govern diverse functions in LV remodelling.119 The strategy of replacement of miRNAs of interest or of blockade of potentially harmful miRNAs (anti-MIRs) is currently being tested in preclinical studies. Whether the use of anti-hypertrophic anti-MIRs could be used in the clinical setting needs to be evaluated.

Exercise

Exercise training in chronic HF may improve symptoms and quality of life, via beneficial effects on endothelial function, central hemodynamics, inflammatory markers, neurohormonal activation, as well as skeletal muscle structure and function. The safety and efficacy of exercise training has been investigated in chronic HFrEF.120 In HFpEF, the Exercise Training in Diastolic Heart Failure–Pilot (Ex-DHF-Pilot) Study121 randomized 64 patients with HFpEF to supervised endurance/resistance training in addition to usual care or to usual care alone. The primary endpoint was the change in peak VO2 after 3 months. Peak VO2 increased with exercise training and remained unchanged with usual care alone. Exercise training was also associated with improvements in the physical functioning score (36-Item Short-Form Health Survey), atrial reverse remodelling and improved left ventricular diastolic function in HFpEF. A larger study examining the effects of exercise training in HFpEF is in progress (http://www.controlled-trials.com/ ISRCTN86879094).

Sodium restriction

Dietary sodium restriction improves ventricular-vascular stiffness and function in hypertensive heart disease. In hypertensive HFPEF patients, a 21-day trial of the sodium-restricted Dietary Approaches to Stop Hypertension (DASH) diet was associated with favourable changes in LV diastolic function, arterial elastance, and LV-arterial coupling in a small clinical study (N=13).122 (Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT00939640).

CONCLUSION

The accurate diagnosis and optimal pharmacological treatment of HFpEF remain challenging. Progress has been made in the understanding of the pathophysiology of this condition, and there is increasing emphasis on therapeutic strategies aimed at altering specific signalling pathways. It is critical for future clinical trials to ensure a proper characterization of the phenotype of patients to be tested. Several novel approaches appear promising in pre-clinical or early clinical studies, but need to be tested in properly designed clinical trials.

REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-1847.
2. Owan TE, Hodge Do, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction (N Engl J Med. 2006;355:251-259.
3. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection in a population-based study. N Engl J Med. 2006;355:260-269.
4. Guidelines for the diagnosis of heart failure. The task force on heart failure of the European Society of Cardiology. Eur Heart J. 1995;16:741-751
5. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail. 2011;13:18-28
6. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004;350:1953-1959.Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 2006;114:2138-2147.
7. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 2006;114:2138-2147.
8. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. Circulation. 1991;84:1589-1596.
9. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: A community-based study. J Am Coll Cardiol. 2009;53:1119-1126.
10. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA. 2002;288:2144-2150.
11. Guder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, Angermann CE, Stork S. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. Circulation.

2007;115:1754-1761.
12. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation. 2011;123:1996-2004.
13. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinc phenotypes within the heart failure spectrum. Circulation. 2011:123:2006-2013; discussion 2014.
14. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005;112:3738-3744.
15. Cleland JG, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F, Freemantle N, Gavazzi A, van Gilst WH, Hobbs FD, Korewicki J, Madeira HC, Preda I, Swedberg K, Widimsky J. Management of heart failure in primary care (the improvement of heart failure programme): an international survey. Lancet. 2002;360:1631-1639.
16. Fukuta H, Little WC. Contribution of systolic and diastolic abnormalities to heart failure with a normal and a reduced ejection fraction. Prog Cardiovasc Dis. 2007;49:229-240
17. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J. 2008;29:1283-1289.
18. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. J Am Coll Cardiol. 2009;54:410-148.
19. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: Exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol. 2009;54:36-46.
20. Drazner MH. The transition from hypertrophy to failure: How certain are we? Circulation. 2005;112:936-938.
21. Gaasch WH, Delorey DE, Kueffer FJ, Zile MR. Distribution of left ventricular ejection fraction in patients with ischemic and hypertensive heart disease and chronic heart failure. Am J Cardiol. 2009;104:1413-1415.
22. Bronzwaer JG, Paulus WJ. Diastolic and systolic heart failure: Different stages or distinct phenotypes of the heart failure syndrome? Curr Heart Fail Rep. 2009;6:281-286.
23. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade

M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: A report from the OPTIMIZE-HF registry. J Am Coll Cardiol. 2007;50:768-777.
24. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: Exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol. 2009;54:36-46.
25. Rame JE, Ramilo M, Spencer N, Blewett C, Mehta SK, Dries DL, Drazner MH. Development of a depressed left ventricular ejection fraction in patients with left ventricular hypertrophy and a normal ejection fraction. Am J Cardiol. 2004;93:234-237.
26. Lam CS, Roger VL, Rodeheffer RJ, Bursi F, Borlaug BA, Ommen SR, Kass DA, Redfield MM. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted county, Minnesota. Circulation. 2007;115:1982-1990.
27. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. JAMA. 2006;296:2209-2216
28. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010;56:845-854.
29. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation. 2005;111:2306-2312.
30. van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van der Velden J, Stienen GJ, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation. 2006;113:1966-1973.
31. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: Implications for systolic and diastolic reserve limitations. Circulation. 2003;107:714-720.
32. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol. 2012;59:442-451.
33. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction:

The CHARM-Preserved trial. Lancet. 2003;362:777-781.
34. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359:2456-2467.
35. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27:2338-2345.
36. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: With emphasis on regional systolic function. Circulation. 2006;113:296-304.
37. Borbely A, van der Velden J, Papp Z, Bronzwaer JG, Edes I, Stienen GJ, Paulus WJ. Cardiomyocyte stiffness in diastolic heart failure. Circulation. 2005;111:774-781.
38. Lopez B, Gonzalez A, Querejeta R, Larman M, Diez J. Alterations in the pattern of collagen deposition may contribute to the deterioration of systolic function in hypertensive patients with heart failure. J Am Coll Cardiol. 2006;48:89-96.
39. van Heerebeek L, Hamdani N, Falcão-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, van der Velden J, Stienen GJ, Laarman GJ, Somsen A, Verheugt FW, Niessen HW, Paulus WJ. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation. 2012;126(7):830-9.
40. López B, González A, Díez J. Circulating biomarkers of collagen metabolism in cardiac diseases. Circulation. 2010;121(14):1645-54.
41. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbély A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation. 2008;117(1):43-51.
42. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation. 2011;124:24-30.
43. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, Redfield MM. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: A community-based study. Circ Heart Fail. 2012;5:710-719.
44. Edelmann F, Stahrenberg R, Gelbrich G, Durstewitz K, Angermann CE, Dungen HD, Scheffold T, Zugck C, Maisch B, Regitz-Zagrosek V,

Hasenfuss G, Pieske BM, Wachter R. Contribution of comorbidities to functional impairment is higher in heart failure with preserved than with reduced ejection fraction. Clin Res Cardiol. 2011;100:755-764.
45. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012;59:998-1005.
46. Packer M. Can brain natriuretic peptide be used to guide the management of patients with heart failure and a preserved ejection fraction? The wrong way to identify new treatments for a nonexistent disease. Circ Heart Fail. 2011;4:538-540.
47. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from dig-pef, charm-preserved, and i-preserve? J Am Coll Cardiol. 2012;60:2349-2356.
48. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. JAMA. 2003;289:194-202.
49. Phan TT, Shivu GN, Abozguia K, Davies C, Nassimizadeh M, Jimenez D, Weaver R, Ahmed I, Frenneaux M. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circ Heart Fail. 2010;3:29-34.
50. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail. 2009;15:782-789.
51. Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, Lakatta EG, Najjar SS, Kass DA. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban baltimore community: The role of atrial remodelling/dysfunction. J Am Coll Cardiol. 2007;49:198-207.
52. Thenappan T, Shah SJ, Gomberg-Maitland M, Collander B, Vallakati A, Shroff P, Rich S. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. Circ Heart Fail. 2011;4:257-265.
53. Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, Ohba K, Matsubara J, Maeda H, Horibata Y, Sakamoto K, Sugamura K, Yamamuro M, Sumida H, Kaikita K, Iwashita S, Matsui K, Kimura K, Umemura S, Ogawa H. Incremental prognostic significance of peripheral

endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol. 2012;60:1778-1786.
54. Maurer MS, King DL, El-Khoury Rumbarger L, Packer M, Burkhoff D. Left heart failure with a normal ejection fraction: Identification of different pathophysiologic mechanisms. J Card Fail. 2005;11:177-187.
55. Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Fu Q, Berk M, Palmer D, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. Circ Heart Fail. 2010;3:617-626.
56. Bench T, Burkhoff D, O'Connell JB, Costanzo MR, Abraham WT, St John Sutton M, Maurer MS. Heart failure with normal ejection fraction: Consideration of mechanisms other than diastolic dysfunction. Curr Heart Fail Rep. 2009;6:57-64.
57. Shah SJ. Matchmaking for the optimization of heart failure with preserved ejection fraction clinical trials: no laughing matter. JACC. 2013, doi: 10.1016/j/jacc.2013.07.010.
58. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation. 2000;101:2118-2121.
59. Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. Prog Cardiovasc Dis. 2005;47:314-319.
60. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: A consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the heart failure and echocardiography associations of the european society of cardiology. Eur Heart J. 2007;28:2539-2550.
61. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, Casey DE, Jr., McMurray JJ, Drazner MH, Mitchell JE, Fonarow GC, Peterson PN, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. J Am Coll Cardiol. 2013.
62. Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, Little WC. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344:17-22.
63. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and

reduced ejection fraction. Circ Heart Fail. 2012;5:720-726.
64. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail. 2013;15:604-613.
65. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: An individual patient data meta-analysis. Eur Heart J. 2012;33:1750-1757.
66. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: A community perspective. Circ Heart Fail. 2008;1:91-97.
67. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pocock S, Pfeffer MA. Effect of candesartan on cause-specific mortality in heart failure patients: The candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) program. Circulation. 2004;110:2180-2183.
68. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE. Mode of death in patients with heart failure and a preserved ejection fraction: Results from the irbesartan in heart failure with preserved ejection fraction study (I-PRESERVE) trial. Circulation. 2010;121:1393-1405.
69. Rickenbacher P, Pfisterer M, Burkard T, Kiowski W, Follath F, Burckhardt D, Schindler R, Brunner-La Rocca HP. Why and how do elderly patients with heart failure die? Insights from the TIME-CHF study. Eur J Heart Fail. 2012;14:1218-1229.
70. Little WC, Brucks S. Therapy for diastolic heart failure. Progress in cardiovascular diseases.2005;47(6):380-388.
71. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux M. Heart failure with preserved ejection fracton is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. JACC. 2009;54(1):36-46.
72. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215-225.
73. Van Veldhuisen DJ, Cohen-Solal A, Böhm M, Anker SD, Babalis d, Roughton M, Coats AJ. Beta-blockade with Nebivolol in Elderly Heart Failure Patients with Impaired and Preserved Left Ventricular Ejection Fraction. Data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure). JACC. 2009;53:2150-2158.

74. Ghio S, Magrini G, Serio A, et al. Effects of nebivolol in elderly heart failure patients with or without systolic left ventricular dysfunction: results of the SENIORS echocardiographic substudy. Eur Heart J. 2006;27(5):562-568.
75. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail. 2012;14(2):219-225.
76. Massie BM, Nelson JJ, Lukas MA, et al., for the COHERE Participant Physicians. Comparison of outcomes and usefulness of carvedilol across a spectrum of left ventricular ejection fraction in patients with heart failure in clinical practice. Am J Cardiol. 2007;99:1263-8.
77. Dobre D, Van Veldhuisen DJ, Dejongste MJL et al. Prescription of beta-blockers in patients with advanced heart failure and preserved ejection fraction. Clinical implications and survival. Eur J Heart Fail. 2007;9:280-6.
78. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. Am J Cardiol. 1990;66:981-986.
79. Lund LH, Benson L, Dahlström, Edner M. Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction. JAMA. 2012;308(20):2108-2117.
80. Ahmed A, Rich MW, Fleg JL et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation. 2006;114:397-403.
81. Anand IS, Rector TS, Cleland JG et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circulation Heart Fail. 2011;4(5):569-577.
82. Cleland JGF, Pelligori P. Defining diastolic heart failure and identifying effective therapies. JAMA. 2013;309:825-826.
83. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) : a randomised trial against atenolol. Lancet. 2002;359 :995-1003.
84. Anjan VY, Loftus TM, Burke MA et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol. 2012;110(6):870-876
85. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction : findings from the Irbesartan

in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ. Heart Fail. 2011;4 :27-35.
86. Krum H, Elsik M, Schneider HG et al. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. Circ Heart Fail. 2011;4(5):561-568.
87. Paulus WJ, Carsten T. A novel paradigm for heart failure with preserved ejection fraction : comorbidities drive myocardial dysfunction and remodelling through coronary microvascular endothelial inflammation. JACC. 2013, doi :10.1016/j.jacc.2013.02.092.
88. Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, Ohba K, Matsubara J, Maeda H, Horibata Y, Sakamoto K, Sugamura K, Yamamuro M, Sumida H, Kaikita K, Iwashita S, Matsui K, Kimura K, Umemura S, Ogawa H. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. JACC. 2012;60(18):1778-86.
89. Lam CS, Brutsaert DL Endothelial dysfunction: a pathophysiologic factor in heart failure with preserved ejection fraction. JACC. 2012;60(18):1787-1789.
90. Oelze M, Knorr M, Kröller-Schön S, Kossmann S, Gottschlich A, Rümmler R, Schuff A, Daub S, Doppler C, Kleinert H, Gori T, Daiber A, Münzel T. Chronic therapy with isosorbide-5-mononitrate causes endothelial dysfunction, oxidative stress, and a marked increase in vascular endothelin-1 expression. Eur Heart J. 2012 May 3. [Epub ahead of print].
91. Zhang M, Koitabashi N, Nagayama T et al. Expression activity and pro-hypertrophic effects of PDE51 in cardiac myocytes. Cell Signal. 2008;20:2231-2236.
92. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011;124(2):164-174.
93. Redfield M, Chen HH, Borlaug BA et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013;309(12):1268-1277.
94. Bondermann D, Pretsch I, Steringer-Mascherbauer R, Rosenkranz S, Tufaro C, Frey R, Ochan M, Kilama S, Unger S, Roessig L, Lang IM. Acute hemoDynamic effects or rIociguat in patients with pulmonary hypertension Associated with diasTolic heart failurE (DILATE-1): a randomized bouble-blind, placebo-controlled, single-dose study. Abstract 3321, ESC Amsterdam 2013.
95. Gu J, Noe A, Chandra P. et al. Pharmacokinetics and pharmacodynamics

of LCZ696, a novel dual-acting Angiotensin Receptor-Neprilysin inhibitor (ARNi). J Clin Pharmacol. 2010;50:401-414.
96. Solomon SD, Zile M, Pieske B et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380(9851):1387-1395.
97. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis and treatment. Eur Heart J. 2011;32(6):670-679.
98. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). J Card Fail. 2011;17(8):634-642.
99. Edelmann F, Wachter R, Schmidt AG, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA. 2013;309(8):781-791.
100. Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. Am Heart J. 2011;162(6):966-972.
101. Phelan D, Thavendiranathan P, Collier P, Marwick TH. Aldosterone antagonists improve ejection fraction and functional capacity independently of functional class: a meta-analysis of randomised controlled trials. BMJ 2012;98:1693-1700.
102. Maltsev VA, Silverman N, Sabbah HN, Undrovinas AI. Chronic heart failure slows late sodium current in human and canine ventricular myocytes: implications for repolarization variability. Eur J Heart Fail. 2007;9(3):219-227.
103. Maier LS, Layug B, Karwatowska E. Ranolazine for the treatment of diastolic heart failure in patients with preserved ejection fraction: the RALI-DHF Proof-of-Concept Study. J Am Coll Cardiol Heart Failure. 2013;1:115-122.
104. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):874-885.
105. Colin P, Ghaleh B, Hittinger L, et al. Differential effects of heart rate reduction and beta-blockade on left ventricular relaxation during exercise. Am J Physiol Heart Circ Physiol. 2002;282(2):H672-H679.
106. Reil JC, Hohl M, Reil GH, et al. Heart rate reduction by If inhibition improves vascular stiffness and left ventricular systolic and diastolic

function in a mouse model of heart failure with preserved ejection fraction. Eur Heart J. 2012–doi.10-1093.
107. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M, Marwick TH. Effect of If-channel inhibition on hemodynamics and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. J Am Coll Cardiol. 2013.
108. Hartog JW, Voors AA, Bakker SJ, Smit AJ, van Veldhuisen DJ. Advanced glycation end-products (AGEs) and heart failure : pathophysiology and clinical implication. Eur J Heart Fail. 2007;9(12):1146-1155.
109. Little WC, Zile MR, Kitzman DW, Hundley WG, O'Brien TX, Degroof RC. The effect of alagebrium chloride (ALT-711), a novel glucose cross-link breaker, in the treatment of elderly patients with diastolic heart failure. J Card Fail. 2005;11(3):191-195.
110. Hattori T, Shimokawa H, Higashi M, et al. Long-term inhibition of Rho-kinase suppresses left ventricular remodelling after myocardial infarction in mice. Circulation. 2004;109 :2234-2239.
111. Martin J, Denver R, Bailey M, Krum H. In vitro inhibitory effects of atorvastatin on cardiac fibroblasts : implications for ventricular remodelling. Clin Exp Pharmacol Physiol. 2005;32:97-701.
112. Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. Circulation. 2005;112:357-363.
113. Tavazzi L, Maggioni AP, Marchioli R et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo controlled trial. Lancet. 2008;372:1231-1239.
114. Lompre AM, Hajjar RJ, Harding SE, Kranias EG, Lohse MJ, Marks AR. Ca2+ cycling and new therapeutic approaches for heart failure. Circulation. 2010;121(6):822-830.
115. Kelly A, Elliott EB, Matsuda R, Kaneko N, Smith GL, Loughrey CM. The effect of K201 on isolated working rabbit heart mechanical function during pharmacologically induced Ca2+ overload. Br J Pharmacol. 2012;165(4b):1068-1083.
116. Jessup M, Greenberg B, Mancini D. Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) : a phase 2 trial of intracoronary gene therapy of sarcoplasmic reticulum Ca2+-ATPase in patients with advanced heart failure. Circulation. 2011;124(3):304-313.
117. Chen J, Wang DZ. microRNAs in cardiovascular development. J Mol Cell Cardiol. 2012;52(5):949-57.
118. van Rooij E. Introduction to the series on microRNAs in the cardiovascular system. Circ Res. 2012;110(3):481-2.
119. Ohtani K, Dimmeler S. Control of cardiovascular differentiation by

microRNAs. Basic Res Cardiol. 2011;106(1):5-11.
120. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS et al. Efficacy and safety of exercise training in patients with chronic heart failure : HF – ACTION randomized controlled trial. JAMA. 2009;301:1439-50]
121. Edelmann F, Gelbrich G, Düngen HD, Fröhling S, Wachter R, Stahrenberg R, Binder L, Töpper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Löffler M, Hasenfuss G, Halle M, Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study.J Am Coll Cardiol. 2011;58(17):1780-91.
122. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, Weder AB, Kovacs SJ, Kolias TJ. Low-sodium DASH Diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. Circ Heart Fail. 2013 Aug 28. [Epub ahead of print].

Chapter 5

Clinical implications for patients with heart failure with preserved ejection fraction

5.1. Patient Selection in Heart Failure With Preserved Ejection Fraction Clinical Trials.

Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, Fiuzat M, Zannad F, Pitt B, O'Connor CM, Lam CS. J Am Coll Cardiol. 2015 Apr 28;65(16):1668-1682

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Disclosures

Dr. Kelly receives funding from the NIH Ruth L. Kirschstein NRSA Institutional Research Training Grant: 5 T32 HL 7101-39. Dr. Mentz has received research support from Gilead Sciences, AztraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Otsuka, Amgen, and ResMed; and honoraria from Thoratec. Dr. Mebazza has received speaker's honoraria from Cardiorentis, Vifor, Edwards, Orion, and Bayer and is a consultant for Adrenomed and Cardiorentis. Dr. Voors has received consultancy fees and/or research grants from Alere, AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Cardio3Biosciences, Celladon, Johnson and Johnson, Merck/MSD, Novartis, Servier, Torrent, Trevena, and Vifor. Dr. Butler has served as a consultant to Amgen, BG Medicine, Celladon, Gambro, Ono Pharma, Trevena, Takada, Bayer HealthCare, Medtronic, CardioCell, Novartis, and GE Healthcare; and has received research support from the National Institutes of Health, European Union, and the Health Resources and Services Administration. Dr Rossig is an employee of Bayer Pharma AG. Dr. Zannad has received grant funding from Novartis, BG Medicine, and Roche Diagnostics, served on a board for Boston Scientific, and served as a consultant for Novartis, Takeda, AstraZeneca, Boehringer-Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and ResMed. Dr. Pitt has received consultancy fees and/or stock options from Pfizer Inc., BayerHealthCare, Lilly, Stealth Peptides, SC Pharmaceuticals, Sarfez Pharmaceuticals, and Relypsa. C.M.O. reports receiving research support from Johnson and Johnson. Drs. Fiuzat and O'Connor have received research support from ResMed. A continuously updated list of disclosure information for C.M.O. is available at https://www.dcri.org/about-us/conflict-of-interest. Dr. Lam has received research support from Boston Scientific, Medtronic, Vifor Pharma, and the National Medical Research Council of Singapore; and is a consultant for Bayer and Novartis. All other authors report no relevant conflicts of interest.

ABSTRACT

Recent clinical trials in patients with heart failure with preserved ejection fraction (HFpEF) have provided important insights into participant selection strategies. Historically, HFpEF trials have included patients with relatively preserved left ventricular ejection fraction ranging from 40 to 55% and a clinical history of heart failure. Contemporary HFpEF trials have also incorporated inclusion criteria such as hospitalization for HFpEF, altered functional capacity, cardiac structure and functional abnormalities and abnormalities in neurohormonal status (e.g. elevated natriuretic peptide levels). Careful analyses of the impact of these patient selection criteria on outcomes in prior trials provide valuable lessons for future trial design. We review recent and ongoing HFpEF clinical trials from a patient selection perspective and appraise trial patient selection methodologies in relation to outcomes. This review reflects discussions between clinicians, scientists, trialists, regulators, and regulatory representatives at the 10th Global CardioVascular Clinical Trialists Forum in Paris, France on December 6, 2013.

Keywords: methodology, HFpEF, clinical trials

Abbreviations: CPET = cardiopulmonary exercise testing, EF = ejection fraction, HF = heart failure; HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LVEDP = left ventricular end diastolic pressure, NP = natriuretic peptide, PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure, VAS-AUC= visual analog scale area under the curve

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) currently represents almost half of all heart failure (HF) patients and is projected to become the predominant form of HF in the future with the growing elderly population. HFpEF represents a large unmet need in cardiovascular medicine(1,2). Over 5 million Americans and 23 million people worldwide have heart failure of which patients with HFpEF constitute more than 50% of these patients and will continue to rise with our aging population(1,3-5). In general, outcomes in HFpEF are similarly poor as patients with heart failure with reduced ejection fraction (HFrEF) with respect to hospitalization and mortality risk. Despite the

therapeutic advances for patients with HFrEF through landmark clinical trials on neurohormonal modulation and device therapy, clinical trials in patients with HFpEF have been challenging and results have been neutral. Important lessons can be learned from these prior trials. In this manuscript, we summarize recent and ongoing HFpEF clinical trials and appraise trial methodologies from the perspective of patient selection in order to critically inform the design of future randomized clinical trials to clinicians, researchers, and patients.

Guideline Definitions for HFpEF

Recommendations for the diagnosis of patients with HFpEF are similar in scope and depth across the most recent US and European guidelines(6-9). The most recent ACC/AHA guidelines defined HFpEF as patients with ejection fraction (EF) ≥50% with symptoms suggestion of HF and exclusion of other potential non-cardiac etiologies of HF. The guidelines also include subpopulations of borderline HFpEF with EF 41-49% and HFpEF with improved EF > 40% for patients previously with reduced EF(6). The 2012 European Society of Cardiology (ESC)

Table 1. Summary of HFpEF Diagnosis Guidelines

Guidelines	Diagnosis
ESC(9)	The following four criteria are required: 1) symptoms typical of HF 2) signs typical of HF 3) normal or only mildly reduced LVEF and LV not dilated and 4) relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction
AHA/ACC(6) – HFpEF	Diastolic HF. Multiple criteria have been used; exclude other potential noncardiac causes of symptoms suggestion of HF.
AHA/ACC – EF 41-49%	Borderline or intermediate EF; these patients have similar characteristics, treatment patterns and outcomes to those with HFpEF
AHA/ACC – improved EF	Patients previously with HFrEF; improved or recovered EF clinically distinct from patients with preserved or reduced EF.
HFSA(7)	Patients with EF ≥50% with symptoms suggestive of HF. Use echocardiography, ECG, stress imaging or cardiac catheterization to distinguish HF with preserved LVEF and other cardiac disorders.

ACC = American College of Cardiology; AHA = American Heart Association; ECG = electrocardiogram;
ESC = indicates European Society of Cardiology; HF = heart failure; HFpEF = heart failure with preserved
ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America
LA = left atrial; LV = left ventricle; LVEF = left ventricular ejection fraction

guidelines defined 4 requirements to diagnose HFpEF, including 1) symptoms typical of HF 2) signs typical of HF 3) normal or only mildly reduced left ventricular ejection fraction without left ventricular dilation and 4) relevant structural heart disease (left ventricular hypertrophy/left atrial enlargement) and/or diastolic dysfunction (Table 1)(8,9).

Definitions in Clinical Trials

The first large clinical trial that focused on patients with HFpEF, the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) Preserved trial, required an EF >40%, New York Heart Association (NYHA) class II-IV symptoms for >4 weeks and any prior hospital admission for a cardiac reason (10). This definition was analogous to HFrEF trials at the time, where EF cut-points of <35% and <45% were used in addition to HF symptoms or known history of HF (11,12). As the results from clinical trials and secondary analyses in these HFpEF populations without use of guideline criteria revealed low event rates and limited benefits from traditional HF therapies, clinical trialists subsequently adjusted entry criteria(13). The EF criterion was increased, echocardiographic parameters were incorporated and eventually natriuretic peptide (NP) levels were included in a combined definition that also required HF symptoms (Table 2). Preserved EF ³50%, symptoms and/or hospitalization for HF, echocardiographic findings and elevated NP levels exemplified the prevailing thought that the underpinning of HFpEF pathophysiology was primarily a disease of elderly women with stiff left ventricles from long-standing hypertension and concomitant diabetes mellitus. However, clinical trials, cohort studies and registry analyses have demonstrated that the HFpEF population is heterogeneous particularly with respect to comorbidities(14). Future clinical trials in HFpEF may benefit from further refinement of these key patient selection criteria in order to optimize the potential for success.

Ejection Fraction

EF was the first inclusion criterion used to differentiate patients with HFrEF from HFpEF. The first three large HFpEF trials studied renin-angiotensin aldosterone system inhibition with EF cut-offs of 40-45%(10,15,16). More recent trials have split between using an EF

Table 2. Inclusion criteria in selected previous and ongoing clinical trials and registries of patients with HFpEF

Trial	Clinical Dx HF	Prior HF Admission	EF %	Atrial Fibrillation/ Atrial Flutter	BNP† pg/ml	NT-proBNP†pg/ml	Event Rate` (1-yr)	Primary Endpoint	Clinical Findings
CHARM-PRESERVED(10)	NYHA II-IV > 4 weeks, hospitalized for cardiac reason, history of hospital admission for cardiac reason	68.8	>40	29.3%	--	--	9.1%	CV death or HF hospitalization	No reduction in CV death; fewer patients in treatment group had HF hospitalization
PEP-CHF(15)	Age ≥70, on diuretics, Echo with DD, 3/9 clinical, 2/4 echo criteria, CV Hospitalization within 6 months	100	>40	22%	--	453	11.96%	Composite of all-cause mortality and unplanned HF Hospitalization	No reduction in all-cause mortality or HF hospitalization
DIG-PEF(84)	NSR, HF symptoms	--	>45	0	--	--	7.8%	Combined HF Hospitalization or HF mortality	Digoxin had no effect on mortality or all-cause CV hospitalization
SENIORS(25)	Age ≥70, HF history + ≥1 of HF hospitalization or EF≤35% within past 6 months	--	>35	37.1%	--	--	19.2%	All-cause mortality or CV hospitalizations	No difference of nebivolol effect on elderly patients with HFpEF vs. HFrEF
I-PRESERVE(16)	NYHA II-IV	44%	≥45	17%	--	320	10.54%	All-cause mortality or CV hospitalization	No improvement from irbesartan in primary endpoints
ELANDD(85)	NYHA II-III, Echo DD	--	>45	--	--	147	--	Change in 6MWD after 6 months	No change in 6MWD or peak VO_2
J-DHF(86)	modified Framingham criteria for HF within 12 months	60%	>40	45.6%	235 – mean	--	8.5	Composite of CV death and unplanned HF hospitalization	No improvement from carvedilol
ALDO-DHF(49)	ambulatory NYHA Class II-III HF, Echo DD	4%	≥50	9%	--	148	--	Co-primary: change in diastolic function (E/e') and peak VO_2 at 12 months	Improved DD but no change in peak VO_2
Ex-DHF(87)	Symptomatic NYHA II-III outpatients, age ≥45, DD grade ≥1, NSR, 1 CV risk factor	--	≥50	--	--	--	--	Change in peak VO_2 after 3 months	Peak VO_2 increased 3.3 ml/min/kg, E/e' and LAVI decreased
PARAMOUNT(18)	NYHA II-IV	45%	≥45	43%	--	>400	n/a	Change in NT-proBNP from BL to 12 weeks	LCZ696 reduced NT-proBNP more than valsartan at 12 weeks
RELAX(48)	Stable outpatients with HF, elevated NT-proBNP or elevated filling pressures, reduced exercise capacity	39%	≥50	50	--	648	12.6	Change in peak VO_2 after 24 weeks of therapy	No improvement in peak VO_2
RELAX-AHF(88)	Admitted for AHF (dyspnea at rest or minimum exertion, pulmonary congestion on chest radiograph & BNP ≥ 350 pg/mL or NT-proBNP ≥ 1400 pg/mL and eGFR 30-75 mL/min per 1.73 m^2	29.5%	≥50	61.2%	--	3992	12.75%‡	Change from BL in VAS AUC to day 5 and proportion of patients with improved dyspnea by Likert scale during 1st 24 h	Improved dyspnea relief by the VAS-AUC and Likert scale
RAAM-PEF(89)	NYHA II-III, clinical HF and BNP ≥100 pg/mL within 2 months	60.9%	≥50	13%	284	--	--	Change in 6MWD	No change in 6MWD
SHIFT-PRESERVED(65)	Signs or Symptoms of HF, Echo with DD, Exercise capacity < 80% age/sex predicted, E/e' > 13 after exercise	--	≥50	--	62	--	--	Exercise capacity, E/e'	Improved peak VO_2 and improved E/e' after exercise
TOPCAT(45)	History of hospitalization within previous 12 months with HF component or elevated BNP within 60 days	71.5%	≥45		>100 235	>360 1017	20.4%	Composite of CV mortality, aborted cardiac arrest or hospitalization for HF	No improvement in composite endpoint
	Enrollment based on HF hospitalization past 1-year	--	--	--	--	--	19.1%	--	--
	Enrollment based on BNP/NT-proBNP criteria	--	--	--	--	--	23.6%	--	--

	Enrollment in the Americas	--	--	--	--	--	12.6%	--	--
	Enrollment in Eastern Europe	--	--	--	--	--	2.3%	--	--
PARAGON-HF	NYHA II-IV requiring treatment with diuretics for ≥30 days, LAE or LVH by echo and HF hospitalization within 9 months or elevated NT-proBNP		≥45			Elevated		composite endpoint of CV death and total HF hospitalizations (first and recurrent)	--
SOCRATES-PRESERVED	Worsening HF requiring hospitalization or IV diuretic as outpatient	--	≥45	--	--	--	--	NT-proBNP from BL to 12 weeks, change of LAVI, safety	--
EDIFY	Stable symptomatic NYHA II-II ≥3 months, HR > 70, E/e' > 13 or e' lateral < 10 cm/s and e' septal < 8 cm/s or LAVI > 34 ml/m^2	--	--	--	≥80	≥220	--	Diastolic function (E/e'), NT-proBNP and 6MWD	--
Ontario, CN(27)	1st time admission for HF (only) based on Framingham HF criteria	--	>50%	31.8	--	--	31.1%	HF survival rate similar between HFrEF and HFpEF	22.2% 1-yr mortality, 13.5% 1-yr readmission for HF, 9.4% 30-d mortality or readmission for HF
Olmsted Co(4)	All consecutive patients hospitalized at Mayo Clinic Hospitals from 1987-2001 (ICD code 428 & DRG code 127)	--	≥50	41.3	--	--	29%	Prevalence and survival of patients with HFpEF over 15 year period	Increased prevalence of HFpEF with similar rate of death over 15 year period
ADHERE(90)	AHF as new-onset HF or decompensated of chronic HF with symptoms requiring hospitalization; ICD-9 discharge diagnosis of HF	63%	≥40	21% (1st ECG)	--	--	2.8%§	Prevalence and outcomes of patients with HFpEF	In-hospital mortality was lower in patients with HFpEF vs. HFrEF.
OPTIMIZE-HF(20)	Hospitalized new-onset or worsening HF as primary cause of admission or significant HF symptoms that developed during hospitalization with HF as primary discharge diagnosis	--	≥40 ≥50	33% 32%	602 537	-- --	35.3%‖ 36.8%‖	Prevalence and outcomes of patients with HFpEF (in-hospital mortality, rehospitalization rate)	HFpEF and HFrEF had similar length of hospital stay, in-hospital morality was lower in HFpEF
MAGGIC(22)	Meta-analysis of observational studies and RCTS through 2006 with eligible studies including patients with HF and death from any cause where EF criterion was not used for study entry	--	≥50	27%	--	--	12.1%¶	Survival of HFpEF vs HFrEF patients	HFpEF patients have a lower risk of death than patients with HFrEF but absolute mortality in HFpEF is still high
GWTG-HF(5)	Hospitalization for acute, decompensated HF based on clinical diagnosis.	54% 56%	≥50 ≥40≤50	34% 34%	551 761	3401 5495	2.5%# 2.3%#	Trend in therapies and outcomes	Hospitalization for HFpEF is increasing relative to HFrEF with in-hospital mortality for HFpEF declining over study period

AHF = acute heart failure; BL = baseline; BNP = brain natriuretic peptide; CV = cardiovascular; DD = diastolic dysfunction; DRG = diagnosis related group; Dx = diagnosis; E/e' = peak early transmitral ventricular filling velocity/early diastolic tissue dopler velocity; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD-9 = international classification of disease; IV = intravenous; LAE = left atrial enlargement; LAVI = left atrial volume index; LVH = left ventricular hypertrophy; mL = milliliter; NSR = normal sinus rhythm; NT-proBNP = N-terminal-pro B-type natriuretic peptide; NYHA = new york heart association; pg = picogram; VAS-AUC = visual analog scale-area under curve; VO2 = peak oxygen consumption; yr = year; 6MWD = 6 minute walk distance

*Data are from placebo groups in clinical trials unless otherwise noted; †Natriuretic peptide levels are median levels unless otherwise specified and if used as inclusion criteria are listed with > or < symbols; ‡RELAX-AHF event rate is cardiovascular death or heart failure/ renal failure hospitalization through Day 60; §ADHERE event rate is in-hospital mortality; ‖OPTIMIZE-HF event rate is post-discharge mortality/rehospitalization at 60-90 days; ¶MAGGIC meta-analysis event rate was number of deaths/100 patient years; #GWTG-HF event rate is in-hospital mortality.

cut-off of ³45% and ³50%. The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) and Treatment of Preserved Cardiac Function HF Aldosterone Antagonist trial (TOPCAT) trials used an EF cut-off for participant inclusion of ³45%(17,18). This cut-off choice between trials in HFrEF and HFpEF have left an intermediate EF group of 10% to 15%% (5,19) of the overall HF population that are largely unstudied with an EF of 40-50%. The CHARM pooled analyses and the American Heart Association's Get With the Guidelines Heart Failure (GWTG-HF) initiative have a bell-shaped EF distribution with 17% (n=1295) and 14% (n=15,184) of patients with an EF of 40-50%, respectively. However, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) Registry and Olmstead County study have a bimodal EF distribution with relatively few patients with an EF of 40-50% suggesting that real-world populations may have fewer patients in this intermediate range than clinical trials(4,19,20). The clinical characteristics and clinical outcomes of patients with an EF between 40-50% appear to be intermediate to patients with HFrEF and HFpEF and the etiology of the mild reduction in EF is unknown (partial EF recovery or primary HFpEF)(21).

It is unknown which EF cut-off provides the most reliable discriminator to enhance the enrollment of the HFpEF phenotype and associated event rates. The MAGGIC meta-analysis demonstrated a clear increase in event rates when EF <40% was compared with >40%(22). The utility of this EF cut-point was also demonstrated in the OPTIMIZE-HF registry, where multivariable analyses revealed in-hospital mortality risk for patients with EF between 40%-50% was similar to those with EF >50%. Specifically, in-hospital mortality decreased 17% for every 10% increase in EF up to 38% with no further association with increased mortality above an EF of 38%(20). The CHARM pooled analyses demonstrated an increased risk for all-cause mortality and cardiovascular death with EF <45%(23). When event rates in the CHARM pooled analyses were evaluated for patients with HFpEF using an EF ³40% and repeating the same analysis with an EF ³50%, the event rates were unchanged (24). A secondary analysis from the Study of the Effects of Nebivolol Intervention on Outcomes

and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial revealed similar primary event rates for patients with HFpEF defined based on an EF >35% or ≥40%(25). The placebo arms of HF clinical trials using lower EF cut-offs such as EF >40% reveal similar event rates as clinical trials with EF cut-offs of ³45% or ³50% (Table 2). Although the event rates from the placebo arms across EF cutoffs from 40–50% are similar, using an EF cut-off of ³40% or ³45% risks including patients with an intermediate EF that may have different characteristics such as more ischemic heart disease.

The historical precedence using EF cut-offs for HFrEF of <40% or ≤ 35% versus ³40, 45, or 50% for HFpEF combined with equal event rates across a range of EFs ³40-50% leaves us with 3 future clinical design options, including, 1) using an EF ³40% to prevent an intermediate EF gap, 2) using a higher EF of ³45 or ³50% and define the created intermediate EF group or 3) lessen the impact of EF as an inclusion criteria. There is no clear absolute EF inclusion criterion; however, insightful use of EF as an inclusion criterion with an eye towards the preferred HFpEF phenotype will lead to successful trials. For example, if a clinical trial is studying a pharmaceutical therapy aimed at HFpEF patients with hypertension and associated structural remodeling, then using a higher EF (e.g. 50%) inclusion criteria will enrich the trial with the preferred phenotype. However, if a promising new therapy appears to work across a more heterogeneous HFpEF population, then using a lower EF (e.g. 40%) inclusion criteria will make the results of the trial generalizable. Ultimately, the appropriate use of EF as an inclusion criteria requires appropriate insight into the HFpEF phenotype that will most benefit from the therapy under investigation.

Prior Heart Failure Hospitalization

Prior hospitalization for HF is a powerful predictor of future outcomes. Investigators pooled the CHARM clinical trials and used a time-updated Cox proportional-hazards model to show that the mortality rate increased after HF hospitalization for upwards of 6 months from time of discharge to randomization (24). This observation was also independent of EF. Longer hospitalization and repeat hospitalization also increased risk of mortality. The time period early after discharge

for hospitalization for HF represents a particularly high-risk window for mortality. This high-risk period may also represent an opportunity to enrich event rates in clinical trials (26). A large population study in Ontario, Canada reported one-year HF readmission rates of 16.1% and 13.5% (p=0.09) for HFrEF and HFpEF, respectively, whereas the unadjusted combined one-year end point of death and HF readmission was 36.1% and 31.1% for HFrEF and HFpEF, respectively (P=0.01) (27). A recent analysis of the CHARM trials revealed that event rates for mortality and hospitalization were higher in patients with previous HF hospitalization compared to those without prior HF hospitalization. Specifically, the time interval between hospitalization and randomization was inversely related and the overall rates between HFrEF and HFpEF were similar (24). Patients hospitalized for HF within the previous 6 months in the placebo arm of the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial had 11.5 events per 100 patient-years compared with 7.0 events per 100 patient-years in those not recently hospitalized for HF(16).

Recent HFpEF trials have incorporated the inclusion criterion of prior hospitalization for HF based on the high risk associated with recent HF hospitalization as identified in the CHARM program (24), but this inclusion criterion has also complicated the interpretation of trial results. The recent TOPCAT trial demonstrated that there were regional differences in how patients entered the trial specifically related to the HF hospitalization criterion. In addition to ³1 sign and symptom of HF, an EF ³45%, and controlled systolic blood pressure, the patients were required to have a history of hospitalization for HF within the previous 12 months or an elevated natriuretic peptide (NP) level within 60 days before randomization (BNP ³100 pg/mL or NT-proBNP ³360 pg/ml). In the Americas, 39.6% of patients qualified for the trial based on HF hospitalization within the preceding 12 months compared with 60.4% of patients from Eastern Europe. Unadjusted Cox models by geographic region and treatment group revealed that patients enrolled in the Americas' control group had a primary outcome event rate of 31.8% compared with 8.4% in patients enrolled in Eastern Europe's control group. Furthermore, post hoc analyses of TOPCAT revealed a four-fold higher event rate between patients enrolled in Russia and

Georgia compared with the Americas, where the primary outcome of cardiovascular death and hospitalization were significantly reduced by spironolactone(28). These data support observations seen in other international clinical trials whereby the patients enrolled in different regions/countries have distinct underlying characteristics, treatment protocols/standards and event rates (17,29-31). Hospitalization for HF is an important inclusion criterion that can drive increased event rates in clinical trials but the clinical definition of HF is subjective with geographical differences in characteristics and standards potentially leading to different event rates.

The use of prior hospitalization as an inclusion criterion in HFpEF clinical trials can and should be a powerful driver of event rates. Using hospitalizations for HF as remote as 12 months has proven to be successful but event rates occur early after discharge; thus, the use of hospitalizations for HF within 6 months will increase event rates. Geographical and international differences in the definition and treatment of patients with HFpEF necessitates further confirmation of clinical HFpEF that can include adjudication or combining HF hospitalization with a specific NP level threshold. Confirming HF hospitalizations or combing HF hospitalization and NP level entry criteria will decrease the variability in HFpEF patients and enrich HFpEF event rates.

Clinical Diagnosis of Heart Failure

HF is a diagnosis based on a clinical assessment and physical examination along with supporting data from the chest radiograph and additional testing. Despite the added clinical and laboratory information, the diagnosis remains largely subjective with clinical gestalt based on history and physical examination and routinely obtained laboratory and hemodynamic measurements. The traditional findings associated with HF including dyspnea, paroxysmal nocturnal dyspnea, jugular venous distension and pulmonary rales have projected sensitivities of 39%, 17% and 29%, respectively, compared with left ventricular dysfunction whereas their specificities are 80%, 98% and 77% respectively(32,33). The NYHA functional class is a subjective measurement used in HF trials that is strongly associated with worse outcomes in patients with HFrEF and HFpEF(34-36). Ultimately, hospitalizing a patient for HF is

determined by the physician's interpretation of the overall patient status. Dyspnea severity is the inherent symptom that influences decision-making. A recent analysis revealed 50% of patients had dyspnea at rest and these patients had increased rates of co-morbidities, mortality and HF readmission risk (37).

There are differences in presentations and management across geographical regions that can challenge the design and interpretation of clinical trial results (38). Dyspnea responds quickly to intravenous diuretics with upwards of 3/4th of patients responding within 6 hours sitting upright vs. 47% supine (39). There are multiple dyspnea scales; commonly used are the five- and the seven point Likert scales and the 10 cm visual analog scale. A post hoc analysis of Ularitide Global Evaluation in Acute Decompensated Heart Failure (URGENT) Dypsnea revealed that up to 40% of patients did not have improved dyspnea in the first 6 hours; for those who did improve, the patient characteristics differed across all three scales with c-index ranging from 0.71 to 0.83, suggesting that improvement in dyspnea may differ from scale to scale (40). The RELAX-AHF trial evaluating serelaxin used a visual analog scale area under the curve (VAS-AUC) endpoint to assess if serelaxin treated patients would have improved dyspnea with baseline dyspnea, congestion on chest radiograph, elevated NP levels to day-5 of the VAS-AUC and the proportion of patients with moderate or marked dyspnea by the Likert scale during the first 24 hours (41). Dyspnea relief measured by VAS-AUC from baseline to Day 5 was improved in the overall population and in HFrEF and HFpEF compared with placebo; however, dyspnea relief at 24 hours using the Likert scale was significantly improved in HFpEF patients compared to placebo but not in HFrEF with treatment (interaction P=0.03). The primary dyspnea endpoint of 448 mm improvement using the VAS-AUC score was significant (P=0.007); however, the co-primary endpoint using the Likert scale endpoint was not significant through 5 days (P=0.7). The dyspnea scoring tools vary from tool to tool and may not always correspond to hard outcomes. The clinical diagnosis of HF based on physician assessment combined with the use axillary tools such as NYHA classification and dyspnea scores will enhance HFpEF clinical trials with patients experiencing HF symptoms. Adding

together dyspnea severity, acute HF diagnostic prediction models, clinical assessment and NP levels have excellent diagnostic accuracy in patients without clear HF(42).

Natriuretic Peptide Levels

NP levels such as BNP and its' co-secreted biologically inactive compound, NT-proBNP are useful markers for diagnosing HF and provide prognostic information for patients presenting with dyspnea. In more recent HFpEF trials, NP levels have been used as key inclusion criteria 1) to increase the specificity of the HFpEF diagnosis; and 2) to select patients at higher risk. Post-hoc analyses from I-PRESERVE trial reveal that NT-proBNP is the most powerful independent factor for the primary outcome of all-cause mortality or cardiovascular hospitalization in patients with HFpEF(43,44). The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial demonstrated an increased number of deaths and hospitalization for HF with higher quartiles of NT-proBNP levels (15). In the TOPCAT trial, patients enrolled based on NP level had primary outcome event rates of 23.6% compared with 19.1% in the placebo group of patients enrolled on the basis of hospitalization in the past year (Table 2)(45). Using NP level thresholds for HFpEF clinical trial entry criteria have driven the HFpEF trials with higher event rates.

The Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) sub-study confirmed that NP levels are lower in patients with HFpEF compared with HFrEF, although the clinical outcomes were similar for a given BNP level (46). NP levels are also markers of the stage of disease and may potentially guide selection of patients in the "modifiable" zone, which identifies patients who may be neither "too well" nor "too sick" to benefit from an intervention. A post-hoc analysis of I-PRESERVE demonstrated that patients with NT-proBNP levels above the median of 339 pg/mL were independently associated with the primary endpoint of all-cause mortality and cardiovascular hospitalizations; whereas, patients with NT-proBNP levels below the median had beneficial effects from irbesartan even after adjustment for 20 covariates (47). In the RELAX trial evaluating phosphodiesterase-5 inhibition in patients with HFpEF, the median NT-

proBNP levels (648 pg/mL) were even higher than in I-PRESERVE with similar results: no improvement in the primary endpoints of peak VO2 or 6 minute walk distance(47,48). The I-PRESEVE and the RELAX trials suggests there is an upper boundary of a modifiable zone above which a more advanced disease state exists where therapies may provide little, if any benefit. In the Aldosterone receptor blockade in Diastolic Heart Failure (ALDO-DHF) trial the median NT-proBNP level of 148 pg/mL demonstrated improvement of one co-primary endpoint, E/e', but no improvement in the other co-primary endpoint, change in peak VO2, suggesting the possibility of a lower boundary in addition to an upper boundary where patients are too well to benefit from therapy (49). The cut-off for NPs provides a distinct opportunity to increase specificity of the diagnosis of HFpEF as well as event rates; however, choosing too high of a level will potentially identify patients too advanced in their disease state to benefit from interventions such as RAAS therapy(46).

NP levels are highly affected by the confounding comorbidities of atrial fibrillation, renal insufficiency and obesity. NP levels are lower in obese patients with HFpEF and independently associated with a favorable adiposity profile(50). Compared with patients with normal BMI, NP levels are significantly lower in obese and overweight patients after adjustment for important clinical characteristics including atrial fibrillation (median values of 227 pg/mL and 608 pg/mL, respectively) (51,52). For example, the NT-proBNP level was revised in the RELAX trial evaluating sildenafil secondary to the "falsely" low NP levels found in obese patients with hemodynamically validated HFpEF. NP levels are known to be higher in patients with atrial fibrillation(53); however, patients with atrial fibrillation and obesity have an inverse relationship between BMI and circulating levels of NT-proBNP suggesting that the underlying pathophysiology of obesity may reduce NP levels(54). HFpEF patients with renal impairment are known to have elevated NP levels with NT-proBNP rising more than BNP; more than 79% of HFpEF patients with BNP levels > 1,000 pg/mL have chronic renal insufficiency(55,56).

Choosing a threshold and ceiling level for trial entry based on NP level requires considering several key factors for success: (1) the trade-off between specificity and sensitivity for the diagnosis of

HFpEF (2) feasibility of patient recruitment (3) clinical setting (acute decompensated HFpEF versus chronic stable HFpEF), and (4) comorbidities. More recent clinical trials have raised the entry criteria level for NP levels for BNP from TOPCAT levels of 100 pg/ml and 360 pg/ml for BNP and NT-proBNP, respectively, to PARAMOUNT's NT-proBNP threshold of 400 pg/ml. The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trials used a cut-off of 150 pg/ml and 600 pg/ml for BNP and NT-proBNP for patients without a HF hospitalization in the previous 12 months and 100 pg/ml and 400 pg/ml, respectively, for patients with a HF hospitalization in the previous 12 months. NP levels are one of the key inclusion criteria that are most specific for patients with HFpEF with resultant increases in event rates. Careful adjustment upward or downward of NP threshold based on comorbidities will enrich the preferred HFpEF phenotype and result in higher event rates.

Atrial fibrillation

Atrial fibrillation is one of the most common comorbidities in patients with HFpEF and co-exists in 21-33% of patients in large registries and 9-61% patients in HFpEF clinical trials (Table 2). HFpEF patients with atrial fibrillation are older, have higher NP levels, larger left atrial volume indexes and are independently associated with death after adjustment for covariates compared with HFpEF patients in sinus rhythm (57). The Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized for Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial is one of many trials with a high enrollment of patients with atrial fibrillation (57%) raising the question as to whether acute symptoms may have been related to exacerbated atrial fibrillation rather than acutely decompensated HFpEF(58). Most drugs targeting HFpEF may not improve patients with a primary problem of atrial fibrillation so studying these patients may confound results and limit our ability to detect HFpEF specific treatment effects. However, entry criteria based on NT-proBNP or LA size would bias for the selection of patients with

atrial fibrillation (who have higher levels of NP and larger LA independent of HF). Furthermore, some have argued that atrial fibrillation should be considered “part and parcel” of the HFpEF disease syndrome since almost two-thirds of HFpEF patients have atrial fibrillation during the course of their disease: approximately 29% of patients with HFpEF have atrial fibrillation before diagnosis, 23% at time of diagnosis and 32% going on to develop atrial fibrillation within 3-4 years of follow-up(57). In PARAMOUNT, the mandate for a NT-proBNP cutoff for entry resulted in an over-representation of patients with atrial fibrillation, in whom patients with higher levels of NT-proBNP are expected related to atrial fibrillation and its resultant increased size of the left atrium and circulatory volume leading to an increased release of NPs. If, as expected, there are more patients with atrial fibrillation without true HFpEF then PARAMOUNT’s goal to detect LCZ696’s efficacy in patients with HFpEF would be significantly impacted as LCZ696 is not known to impact the underlying pathophysiology of atrial fibrillation. The significant number of enrolled patients with atrial fibrillation led to a cap on the absolute percentage of patients with atrial fibrillation that could be recruited.

Strategies to address this dilemma include: 1) introduction of a cap on the proportion of patients with atrial fibrillation who can be recruited; and 2) using different NT-proBNP cutoffs for those with and without atrial fibrillation.

Hemodynamics

Hemodynamics measured invasively and noninvasively yield an objective assessment of pressures in the venous circulation. Central venous pressure increases when increased circulatory volume occurs from tricuspid regurgitation or right ventricle failure, and can be estimated fairly accurately through echocardiography. Hemodynamic measurements help discern which patients have the diagnosis of HF when the usual selection criteria are not conclusive. Pulmonary hypertension is frequently caused by left-sided HF and defined as pulmonary artery systolic pressure (PASP) >35 mmHg derived from the tricuspid velocity is highly prevalent with estimates as high as 83% of patients with HFpEF (59), whereas pulmonary capillary wedge

pressure (PCWP) is estimated from the ratio of early transmitral flow velocity to early mitral annular diastolic velocity. Normal filling pressures and other hemodynamic parameters such as PCWP, PASP and left ventricular end diastolic pressure (LVEDP) at rest followed by normal filling pressures during exercise excludes the diagnosis of HF. However, if the filling pressures increase in proportion to the increase in PCWP, then a diagnosis of HFpEF is suggested(60-62). Other related diagnoses such as pulmonary arterial hypertension can also be clearly identified during right heart catheterization.

However, outside of small studies evaluating hemodynamics in patients with equivocal diagnoses, invasive hemodynamic measurements are infrequently used and there is limited data from clinical trials that confirm these measurements enhance event rates. The RELAX trial evaluating phosphodiesterase-5 inhibition utilized an alternative entry criteria for elevated LVEDP or PCWP if other criteria were not met in a small number of unreported patients(48). Cardiopulmonary exercise testing (CPET) provides additive information to hemodynamics that may help exclude HF with normal tests and confirm or suggest a HF diagnosis with abnormal results(63). CPET measurements obtained during exercise include the gas exchange parameters peak oxygen consumption (VO2) and the slope of the relationship between ventilation and carbon dioxide production (Ve/VCO2 slope) are independently associated with mortality and are strong independent predictors of mortality(36). A study evaluating serelaxin demonstrated significant reductions in peak PCWP without changes in cardiac index and a CPET with echocardiography study in HFpEF patients treated with ivabradine revealing improved METS, peak VO2 and reduced E/e' provided the impetus to pursue larger clinical trials on these two promising therapies(64,65).

Guazzi and colleagues demonstrated significant improvements in mean pulmonary artery pressure, right atrial pressure, pulmonary vascular resistance, tricuspid annular systolic excursion and EF using invasive hemodynamics obtained in forty-four patients with HFpEF randomized to placebo or sildenafil with benefits through 12 months of follow-up in patients with baseline evidence of chronically elevated left ventricular filling pressures(66). Guazzi's work led to further investigation

of sildenafil's phosphodiesterase-5 inhibition in the RELAX clinical trial of 216 patients with end-points closely related to hemodynamics: change in peak VO2 and 6-minute walk distance(48). After 24 weeks, there was no significant changes in peak VO2 or change in 6-minute walk distance; however, hemodynamic related measurements of E/e', left atrial volume index and PASP were consistent with chronically elevated left ventricular filling pressures. Cardiovascular hemodynamics obtained from noninvasive and invasive measurements are very helpful for the confirmation or exclusion patients who do not meet diagnostic criteria from the usual selection criteria. However, the actual impact hemodynamic measurements add to driving event rates in clinical trials remain unknown and future inclusion in pilot studies and clinical trials are needed to verify their value.

Lessons Learned

HF remains a clinical diagnosis that may be enhanced by weighing and/or limiting the patient selection criteria discussed herein including EF, prior HF hospitalization, natriuretic peptide levels, comorbidities such as atrial fibrillation, clinical diagnosis of HF and hemodynamics (Figure 1). In addition to balancing patient selection criteria, clinical trial

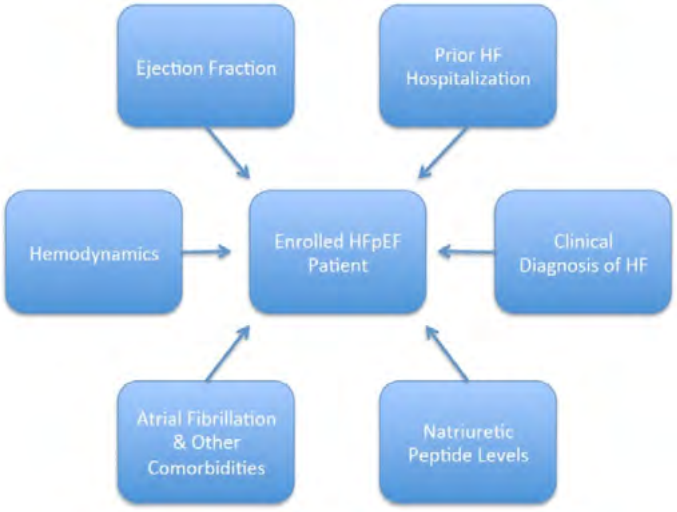

Figure 1. Inclusion Criteria that alter event rates in HFpEF Clinical Trials. Representative inclusion criteria used in past, present and future clinical trials of patients with HFpEF. HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

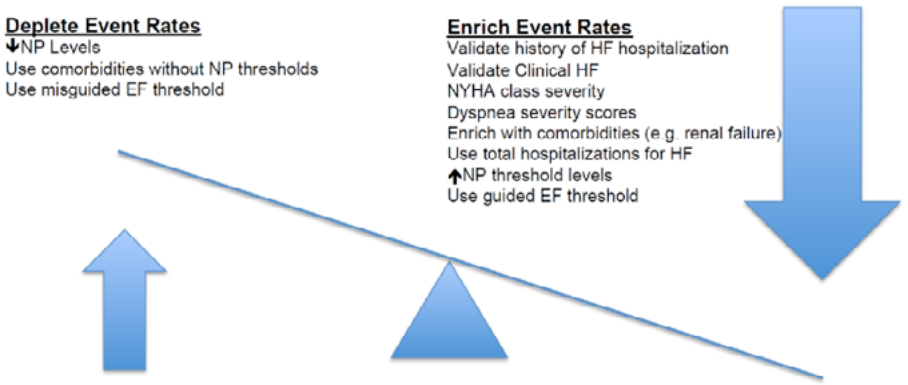

Figure 2. Strategies to enrich event rates in HFpEF Clinical Trials. The appropriate use of specific inclusion criteria and targeted thresholds will facilitate the reduction or enrichment of event rates in well-designed clinical trials of patients with HFpEF. EF = ejection fraction; HF = heart failure; NP = natriuretic peptide. _= higher; _= lower.

design, implementation and integration of novel diagnostic techniques are paramount to discovering future therapies for HFpEF (Figure 2). Enrolling patients quickly prevents cross over to the treatment intervention as evidenced by a restrictive analysis of PEP-CHF that trended towards clinical significance (p=0.055) for the primary endpoint of all-cause mortality and unplanned HF hospitalization in the first year with the secondary endpoint of unplanned hospitalization for HF significant (p=0.033)(15). Implementing important patient centered outcomes through the use of all hospitalizations instead of only first hospitalizations can drive important event rates (67). Factoring in the expected differences in event rates across geographical and international regions based on past event rates related to differences in clinical and socioeconomic practices across the world (Table 2) as evidenced by post-hoc analyses from TOPCAT trial demonstrating clinical benefit in the Americas (HR 0.82) compared with Russia/ Republic of George (HR 1.1) will allow for proper statistical power to detect meaningful differences(28,45).

Recent studies evaluating new imaging techniques measuring impaired systolic function in patients with HFpEF through 3D speckle, left atrial, and longitudinal strain analyses are associated with mortality and may

provide opportunities to enhance patient selection and event rates (68-73). Emerging and novel biomarkers such as cystatin C, galectin-3 and growth differentiation factor-15 may help phenotype, risk stratify and identify patients with or at risk for HFpEF(74-76). Evidence continues to mount from studies evaluating isolated comorbidities such as coronary disease(77) and diabetes mellitus(78) in patients with HFpEF demonstrating worse mortality through splitting the heterogeneous HFpEF population into targeted groups into distinct phenotypes may lead to therapeutic advances(79,80) Shah and colleagues recently used statistical learning algorithms in 400 patients with HFpEF to perform an unbiased clustering analysis of dense phenotypic data to “phenomap” patients with HFpEF into more homogeneous subclasses(81). Combinations of ‘omics, cluster analyses and phenomapping result in novel classifications of HFpEF that may simplify this heterogeneous population into discernable classifications that ultimately allow targeted pharmaceutical therapies(82,83). Integration of the past lessons learned of current patient selection criteria from previous HFpEF clinical trials with emerging and novel imaging, biomarker and phenotype classification schema provide a unique scaffold to advance HFpEF clinical trial success.

Conclusions

Promising new therapeutic options based on sound scientific rationale and observational data, such as the recently published study on angiotensin-neprilysin inhibitors, may prove to benefit patients with HFpEF. However, clinical trials in HFpEF using standard, mortality-reducing therapies known to HFrEF have thus far been neutral. In order to optimize clinical trial effectiveness, trials in patients with HFpEF must define a clear target population through the balanced use of the following key inclusion and exclusion criteria: universal EF cut-point, appropriate NP level thresholds, limited number of patients with atrial fibrillation (with a higher NP cut-point), use of a clearly defined history of HF and diagnosis of previous HF (Central Illustration). Attaining hemodynamic measurements related to HFpEF through use of echocardiography, cardiopulmonary exercise testing, and invasive hemodynamics may complement or validate challenging patients.

Thoughtful clinical trial design that incorporates the lessons learned from previous and ongoing clinical trials in patients with HFpEF will provide the trial landscape necessary to determine if future therapies actually improve the outcomes and/or quality of life in patients with HFpEF.

Central Illustration. Methodologic Recommendations to Enhance Clinical Trial Success Through Increased Event Rates

EF threshold	Use an EF cutoff ≥50% to reduce the number of patients who may represent a different disease phenotype such as patients who have recovered their EF
NP Levels	Use NT-proBNP entry criteria threshold and limits to choose patients with the most modifiable substrate to maximize ideal event capture rates eliminating patients with less modifiable substrates.
HF hospitalization	Clearly define prior hospitalization for HF with a validation cohort and/or model to enrich event rates and facilitate standardized clinical trials for easier trial comparison and shared lessons learned
Comorbidities	Limit the number of patients with comorbidities such as atrial fibrillation through use of a higher natriuretic peptide level entry criteria with a cap on the total number of patients with atrial fibrillation to focus on a more accurate HFpEF phenotype
Clinical HF diagnosis	Clearly define the clinical diagnosis of heart failure for a unified, accurate HFpEF phenotype across international and geographical regions.
Hemodynamics	Use invasive/noninvasive hemodynamics and CPET measurements in smaller populations or subgroups to investigate and/or prove new concepts and confirm or exclude unclear diagnoses
Clinical Trial Design	Include important patient-centered endpoints such as use of all hospitalizations instead of only first hospitalization to enhance important clinical and regulatory endpoints.

Previous and ongoing clinical trial inclusion criteria and methodologic considerations are presented with recommendations to highlight the complexity of clinical trial design with associated recommendations to enhance event rates and future clinical trial success. CPET = cardiopulmonary exercise testing; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; NP= natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Central Illustration. Methodologic Recommendations to Enhance Clinical Trial Success Through Increased Event Rates. Previous and ongoing clinical trial inclusion criteria and methodologic considerations are presented with recommendations to highlight the complexity of clinical trial design with associated recommendations to enhance event rates and future clinical trial success. CPET = cardiopulmonary exercise testing; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; NP= natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL et al. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014;129:399-410.
2. Tate S, Griem A, Durbin-Johnson B, Watt C, Schaefer S. Marked elevation of B-type natriuretic peptide in patients with heart failure and preserved ejection fraction. J Biomed Res 2014;28:255-61.
3. McMurray JJ, Petrie MC, Murdoch DR, Davie AP. Clinical epidemiology of heart failure: public and private health burden. Eur Heart J 1998;19 Suppl P:P9-16.
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
5. Steinberg BA, Zhao X, Heidenreich PA et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 2012;126:65-75.
6. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.
7. Lindenfeld J, Albert NM, Boehmer JP et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Cardiac Fail 2010;16:e1-194.
8. Dickstein K, Cohen-Solal A, Filippatos G et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388-442.
9. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
10. Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-81.
11. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med

1987;316:1429-35.
12. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. N Engl J Med 1992;327:685-91.
13. Paulus WJ, van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! J Am Coll Cardiol 2010;55:526-37.
14. Mentz RJ, Kelly JP, von Lueder TG et al. Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction. J Am Coll Cardiol 2014;64:2281-2293.
15. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-45.
16. Massie BM, Carson PE, McMurray JJ et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-67.
17. McMurray JJ, O'Connor C. Lessons from the TOPCAT trial. N Engl J Med 2014;370:1453-4.
18. Solomon SD, Zile M, Pieske B et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387-95.
19. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail 16:1049-55.
20. Fonarow GC, Stough WG, Abraham WT et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768-77.
21. Gottdiener JS, McClelland RL, Marshall R et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002;137:631-9.
22. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;33:1750-7.
23. Solomon SD, Anavekar N, Skali H et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005;112:3738-44.
24. Bello NA, Claggett B, Desai AS et al. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. Circ Heart Fail 2014;7:590-5.
25. van Veldhuisen DJ, Cohen-Solal A, Bohm M et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With

Heart Failure). J Am Coll Cardiol 2009;53:2150-8.
26. Solomon SD, Dobson J, Pocock S et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 2007;116:1482-7.
27. Bhatia RS, Tu JV, Lee DS et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260-9.
28. Pfeffer MA, Claggett B, Assmann SF et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation 2015;131:34-42.
29. Mentz RJ, Kaski JC, Dan GA et al. Implications of geographical variation on clinical outcomes of cardiovascular trials. Am Heart J 2012;164:303-12.
30. O'Connor CM, Fiuzat M, Swedberg K et al. Influence of global region on outcomes in heart failure beta-blocker trials. J Am Coll Cardiol 2011;58:915-22.
31. Kristensen SL, Kober L, Jhund PS et al. International Geographic Variation in Event Rates in Trials of Heart Failure With Preserved and Reduced Ejection Fraction. Circulation 2015;131:43-53.
32. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? QJM: Monthly Journal of the Association of Physicians 1997;90:335-9.
33. Gillespie ND, McNeill G, Pringle T, Ogston S, Struthers AD, Pringle SD. Cross sectional study of contribution of clinical assessment and simple cardiac investigations to diagnosis of left ventricular systolic dysfunction in patients admitted with acute dyspnoea. BMJ 1997;314:936-40.
34. Madsen BK, Hansen JF, Stokholm KH, Brons J, Husum D, Mortensen LS. Chronic congestive heart failure. Description and survival of 190 consecutive patients with a diagnosis of chronic congestive heart failure based on clinical signs and symptoms. Eur Heart J 1994;15:303-10.
35. Ahmed A, Aronow WS, Fleg JL. Higher New York Heart Association classes and increased mortality and hospitalization in patients with heart failure and preserved left ventricular function. Am Heart J 2006;151:444-50.
36. Russell SD, Saval MA, Robbins JL et al. New York Heart Association functional class predicts exercise parameters in the current era. Am Heart J 2009;158:S24-30.
37. Mentz RJ, Mi X, Sharma PP et al. Relation of dyspnea severity on admission for acute heart failure with outcomes and costs. Am J Cardiol 2015;115:75-81.

38. Collins SP, Pang PS, Lindsell CJ et al. International variations in the clinical, diagnostic, and treatment characteristics of emergency department patients with acute heart failure syndromes. Eur J Heart Fail 2010;12:1253-60.
39. Mebazaa A, Pang PS, Tavares M et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J 2010;31:832-41.
40. Pang PS, Collins SP, Sauser K et al. Assessment of dyspnea early in acute heart failure: patient characteristics and response differences between likert and visual analog scales. Acad Emerg Med 2014;21:659-66.
41. Teerlink JR, Cotter G, Davison BA et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013;381:29-39.
42. Steinhart B, Thorpe KE, Bayoumi AM, Moe G, Januzzi JL, Jr., Mazer CD. Improving the diagnosis of acute heart failure using a validated prediction model. J Am Coll Cardiol 2009;54:1515-21.
43. McKelvie RS, Komajda M, McMurray J et al. Baseline plasma NT-proBNP and clinical characteristics: results from the irbesartan in heart failure with preserved ejection fraction trial. J Card Fail 2010;16:128-34.
44. Komajda M, Carson PE, Hetzel S et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). Circ Heart Fail 2011;4:27-35.
45. Pitt B, Pfeffer MA, Assmann SF et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.
46. van Veldhuisen DJ, Linssen GC, Jaarsma T et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol 2013;61:1498-506.
47. Anand IS, Rector TS, Cleland JG et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. Circ Heart Fail 2011;4:569-77.
48. Redfield MM, Chen HH, Borlaug BA et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268-77.
49. Edelmann F, Wachter R, Schmidt AG et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 2013;309:781-91.

50. Neeland IJ, Winders BR, Ayers CR et al. Higher natriuretic peptide levels associate with a favorable adipose tissue distribution profile. J Am Coll Cardiol 2013;62:752-60.
51. Wang TJ, Larson MG, Levy D et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109:594-600.
52. Stavrakis S, Pakala A, Thomas J, Chaudhry MA, Thadani U. Obesity, brain natriuretic peptide levels and mortality in patients hospitalized with heart failure and preserved left ventricular systolic function. Am J Med Sci 2013;345:211-7.
53. Liu Y, Xiao Y, Chen X, Zhang F. Association between plasma brain natriuretic peptide/N-terminal pro-brain natriuretic peptide levels and atrial fibrillation: evidence from a meta-analysis. Chin Med J 2014;127:2824-8.
54. Zheng LH, Wu LM, Yao Y et al. Impact of body mass index on plasma N-terminal ProB-type natriuretic peptides in Chinese atrial fibrillation patients without heart failure. PloS one 2014;9:e105249.
55. Agoston I, Cameron CS, Yao D, Dela Rosa A, Mann DL, Deswal A. Comparison of outcomes of white versus black patients hospitalized with heart failure and preserved ejection fraction. Am J Cardiol 2004;94:1003-7.
56. Takase H, Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship. Eur J Clin Invest 2014;44:303-8.
57. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation 2013;128:1085-93.
58. Massie BM, O'Connor CM, Metra M et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419-28.
59. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol 2009;53:1119-26.
60. Andersen MJ, Borlaug BA. Invasive hemodynamic characterization of heart failure with preserved ejection fraction. Heart Fail Clin 2014;10:435-44.
61. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588-95.
62. Paulus WJ, Tschope C, Sanderson JE et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and

Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-50.
63. Lainchbury JG, Richards AM. Exercise testing in the assessment of chronic congestive heart failure. Heart 2002;88:538-43.
64. Ponikowski P, Mitrovic V, Ruda M et al. A randomized, double-blind, placebo-controlled, multicentre study to assess haemodynamic effects of serelaxin in patients with acute heart failure. Eur Heart J 2014;35:431-41.
65. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M, Marwick TH. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. J Am Coll Cardiol 2013;62:1330-8.
66. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation 2011;124:164-74.
67. Rogers JK, Pocock SJ, McMurray JJ et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail 2014;16:33-40.
68. Kowallick JT, Kutty S, Edelmann F et al. Quantification of left atrial strain and strain rate using Cardiovascular Magnetic Resonance myocardial feature tracking: a feasibility study. J Cardiovasc Magn Reson 2014;16:60.
69. Kraigher-Krainer E, Shah AM, Gupta DK et al. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:447-56.
70. Luo XX, Fang F, Lee AP et al. What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? Int J Cardiol 2014;172:132-7.
71. Stampehl MR, Mann DL, Nguyen JS, Cota F, Colmenares C, Dokainish H. Speckle Strain Echocardiography Predicts Outcome in Patients with Heart Failure with both Depressed and Preserved Left Ventricular Ejection Fraction. Echocardiography 2014.
72. Wang J, Fang F, Wai-Kwok Yip G et al. Left ventricular long-axis performance during exercise is an important prognosticator in patients with heart failure and preserved ejection fraction. Int J Cardiol 2014;178c:131-135.
73. Izumiya Y, Hanatani S, Kimura Y et al. Growth differentiation factor-15 is a useful prognostic marker in patients with heart failure with preserved ejection fraction. Can J Cardiol 2014;30:338-44.
74. Carrasco-Sanchez FJ, Galisteo-Almeda L, Paez-Rubio I et al. Prognostic value of cystatin C on admission in heart failure with preserved ejection fraction. J Card Fail 2011;17:31-8.

75. Gullestad L, Ueland T, Kjekshus J et al. Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Eur Heart J 2012;33:2290-6.
76. de Boer RA, Edelmann F, Cohen-Solal A, Mamas MA, Maisel A, Pieske B. Galectin-3 in heart failure with preserved ejection fraction. Eur J Heart Fail 2013;15:1095-101.
77. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:2817-27.
78. Lindman BR, Davila-Roman VG, Mann DL et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol 2014;64:541-9.
79. Maurer MS, Mancini D. HFpEF: Is Splitting Into Distinct Phenotypes by Comorbidities the Pathway Forward? J Am Coll Cardiol 2014;64:550-2.
80. Greenberg B. Heart failure preserved ejection fraction with coronary artery disease: time for a new classification? J Am Coll Cardiol 2014;63:2828-30.
81. Shah SJ, Katz DH, Selvaraj S et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation 2015;131:269-79.
82. Ahmad T, Pencina MJ, Schulte PJ et al. Clinical Implications of Chronic Heart Failure Phenotypes Defined by Cluster Analysis. J Am Coll Cardiol 2014;64:1765-74.
83. Shah SJ, Katz DH, Deo RC. Phenotypic Spectrum of Heart Failure with Preserved Ejection Fraction. Heart Fail Clin 2014;10:407-418.
84. Ahmed A, Rich MW, Fleg JL et al. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. Circulation 2006;114:397-403.
85. Conraads VM, Metra M, Kamp O et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail 2012;14:219-25.
86. Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 2013;15:110-8.
87. Edelmann F, Gelbrich G, Dungen HD et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780-91.
88. Filippatos G, Teerlink JR, Farmakis D et al. Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial. Eur Heart J 2014;35:1041-50.

89. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). J Card Fail 2011;17:634-42.
90. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76-84.

Summary and conclusions

Summary

The body of work covered in this thesis have established that:

HFpEF is highly prevalent, constitutes at least half the global burden of heart failure; and carries a prognosis as poor as most cancers. As a condition mainly affecting elderly women, its burden is increasing to epidemic proportions in aging societies, where it is becoming the predominant form of heart failure. Yet in sharp contrast to the wealth of effective therapies for heart failure with reduced ejection fraction, there is still no proven therapy to improve survival in HFpEF. A chief obstacle to therapeutic advancement is the continued lack of understanding of underlying pathophysiologic pathways that may be targeted by novel therapies. As a result, outcomes in HFpEF have not improved for decades and it is now the greatest unmet need in cardiovascular medicine (chapters 1& 2).

The pathophysiology of HFpEF goes beyond left ventricular diastolic dysfunction, and also involves systolic ventricular-vascular stiffening, myocardial contractile dysfunction (in spite of overall preserved chamber ejection fraction), pulmonary hypertension with intrinsic pulmonary vascular disease, and even non-cardiovascular organ system dysfunction such as pulmonary dysfunction. A unifying mechanism underlying the myriad manifestation in HFpEF may be endothelial dysfunction with resultant microvascular inflammation and ischemia, leading to fibrosis and end organ dysfunction in multiple body systems (chapter 3).

The unique predisposition of women to HFpEF may be explained by exaggerated ventricular-vascular responses to triggers such as pressure overload. The important roles of atrial fibrillation and renal dysfunction in HFpEF are underscored by the particularly poor prognosis among women with HFpEF and these co-existing conditions (chapter 4).

Recognition of the heterogeneity of HFpEF and potential mechanisms

beyond cardiac diastolic dysfunction is critical for the design of clinical trials in HFpEF. Ongoing clinical trials targeting endothelial dysfunction and the nitric oxide – cyclic guanylate monophosphate – phosphokinase G axis offer hope for improving outcomes in HFpEF (chapter 5).

Perspectives

The knowledge gained from these studies have challenged prior concepts, addressed several gaps, and provided novel insights into the syndrome of HFpEF.

Whereas heart failure was traditionally viewed as synonymous with pump failure (i.e. reduced ejection fraction or HFrEF), careful epidemiologic review (chapter 2) revealed that heart failure occurred in the setting of normal pump function with equal frequency. In fact an analysis of epidemiologic trends over time showed that the prevalence of HFpEF was increasing relative to that of HFrEF. At the same time, the survival in HFpEF had not improved over the last decade, in sharp contrast to the improvements observed with HFrEF. These data reflected the lack of effective therapies in HFpEF, and underscored the urgent need for better understanding of key pathophysiologic targets in HFpEF.

Several key observations from the epidemiologic studies in chapter 2 provided the rationale for the in-depth studies in chapters 3 & 4. The initial term “diastolic heart failure” was coined to reflect the belief that diastolic dysfunction was the underlying mechanism responsible for the syndrome. However, asymptomatic diastolic dysfunction was found to be highly prevalent even in the absence of heart failure among individuals within the general community, and particularly in the elderly and those with systemic hypertension (both key risk factors for HFpEF). This called for careful studies comparing HFpEF with age- and comorbidity- matched controls without HFpEF (chapter 3). Furthermore, the prominence of non-cardiac deaths in HFpEF, as well as the striking female predisposition to HFpEF (women outnumbering men by 2:1), called for assessment of the role of non-cardiac comorbidities in the

pathophysiology of HFpEF (chapter 3) and further studies on sex-specific mechanisms (chapter 4).

We provided the first population-based evidence that, compared to age- and sex- matched controls with hypertension but without heart failure, more severe diastolic dysfunction was present in HFpEF, thus supporting a key role for worsening diastolic dysfunction in the progression from asymptomatic hypertensive heart disease to HFpEF (Lam Circulation 2007). These cross-sectional findings were later supported by longitudinal evidence from the Framingham Heart Study showing that asymptomatic diastolic dysfunction preceded and predicted the future onset of HFpEF (Lam Circulation 2011). However these studies also challenged prior concepts by showing a prominent presence of systolic ventricular-vascular stiffening (Lam Circulation 2007) and occult myocardial contractile dysfunction despite an overall preserved ejection fraction (Borlaug, Lam JACC 2009) in HFpEF, and establishing that beyond cardiac dysfunction, pulmonary dysfunction also predicted the onset of future HFpEF (Lam Circulation 2011). In fact, intrinsic pulmonary vascular disease was present in HFpEF, and pulmonary hypertension was a potent independent predictor of survival, indicating its pathophysiologic role in HFpEF progression (Lam JACC 2009). This opened the door to therapeutic approaches targeting pulmonary arterial hypertension in HFpEF (e.g. phosphodiesterase-5 inhibitors).

Further insights were provided by studying sex differences in HFpEF (chapter 4). The importance of left ventricular remodeling response to a common trigger (pressure overload) was demonstrated in these studies, where women displayed more concentric cardiac remodeling compared to men with HFpEF (Gori, Lam Eur J Heart Fail 2014). Additionally, atrial fibrillation and renal dysfunction were shown to be key drivers of poor outcomes in HFpEF, particularly among women (Circ Heart Fail 2012). Ongoing studies are now addressing these 2 factors in remaining questions such as cause versus effect and interaction with age and sex in the pathogenesis and progression of HFpEF. Answers to these important questions will inform future clinical trial design and

the potential to treat HFpEF by treating its comorbidities (chapter 5).

Tying things together around a unifying concept, a central role of endothelial dysfunction, microvascular inflammation and the nitric oxide – cyclic guanylate monophosphate – phosphokinase G axis has emerged (Lam JACC 2012, Paulus and Tschöpe JACC 2013). This paradigm shift carries great clinical significance in that: (1) HFpEF is viewed as a systemic disease (rather than isolated left ventricular diastolic dysfunction); (2) the important role of comorbidities is acknowledged; (3) novel therapeutic approaches targeting this axis (e.g. soluble guanylate cyclase stimulators) have now surfaced and are being tested in ongoing clinical trials (chapter 5).

Conclusions

Much progress has been made over the last decade in the recognition and understanding of HFpEF: from questioning its existence to acknowledgement of its prominence as one of the greatest unmet needs in cardiology today; from viewing it as pure “diastolic heart failure” to an understanding of the myriad non-diastolic and even non-cardiac mechanisms that contribute to its pathophysiology; and from blindly extrapolating therapies from HFrEF to the development of novel approaches targeted at key underlying pathways.

Yet our work is far from done. We have yet to achieve improvements in outcomes in randomized controlled clinical trials for HFpEF, and international guidelines for HFpEF have remained unchanged for decades. Ongoing trials offer hope. Future research into endothelial-myocyte cross-talk, microvascular ischemia and microvascular inflammation may provide further therapeutic targets (Lim, Lam Eur Heart J. 2015 Apr 23. pii: ehv132. [Epub ahead of print]).

Acknowledgements

This thesis is dedicated to my beloved husband James Hare and my son Jordan Kuan Hare.